FLOMAX® Capsules
(tamsulosin hydrochloride)

ACADEMY OF MANAGED CARE PHARMACY (AMCP)

FORMULARY DOSSIER

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

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1 INTRODUCTION

The purpose of this formulary submission dossier is to present the clinical and economic rationale to support the acceptance and use of Flomax® (tamsulosin hydrochloride) in the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Flomax® is a selective α_{1A}-adrenoceptor antagonist that is prescribed orally once daily. This dossier presents the ways in which Flomax adds value to the current management of BPH, both in terms of clinical effectiveness and economic efficiency.

Section 2 provides a description of Flomax® (including a cross-label comparison with its main competitors, Hytrin®, Cardura®, Proscar®, Avodart®), BPH, and its management.

Section 3 provides a summary of the supporting clinical and pharmacoeconomic evidence for Flomax based on results from the Flomax® clinical trial program.

Section 4 provides a report of an economic model developed to evaluate the cost-effectiveness of Flomax® versus doxazosin and terazosin as initial treatment for moderate BPH over a two-year time horizon from a payer perspective.

Section 5 provides a summary of the clinical and economic value of Flomax®.

2 PRODUCT INFORMATION

2.1 Product description

Generic name:	tamsulosin hydrochloride
Brand name:	Flomax®
Therapeutic class:	α_1-adrenoceptor antagonist
Approval date:	04/15/1997

Flomax® (tamsulosin hydrochloride) is an antagonist of alpha$_{1A}$ adrenoceptors in the prostate. The chemical name of Flomax® is (-)-(R)-5-[[2-(0-ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride (see entire Flomax® label in Section 6).

Approved Indications

Flomax® capsules are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Flomax capsules are not indicated for the treatment of hypertension.

How Supplied

Flomax® capsules 0.4 mg are supplied in high density polyethylene bottles containing 100 (NDC 0597-0058-01; AWP $201.23 per bottle, $2.01 per day) hard gelatin capsules with olive green opaque cap and orange opaque body. The capsules are imprinted on one side with "Flomax 0.4 mg" and on the other side with "BI 58."

Dosage and Administration

The recommended dose is one 0.4 mg capsule given once daily. It should be administered approximately one-half hour following the same meal each day. For those patients who fail to respond to the 0.4 mg dose after two to four weeks of dosing, the dose can be increased to 0.8 mg once daily. If administration is discontinued or interrupted for several days at either the 0.4 mg or 0.8 mg dose, therapy should be started again with the 0.4 mg once daily dose.

Cross-Label Comparison of Flomax® and Main Comparators

The main comparators for Flomax® are Hytrin® (terazosin hydrochloride), Cardura® (doxazosin mesylate), Proscar® (finasteride), and Avodart® (dutasteride). The product information documents for all four drugs are summarized in Table 1.

Table 1. Cross-label Comparisons for Products Used in Treatment of BPH

	Flomax® (tamsulosin hydrochloride)	**Hytrin® (terazosin hydrochloride)**	**Cardura® (doxazosin mesylate)**	**Uroxatral™ (alfuzosin hydrochloride)**
Empirical formula	$C_{20}H_{28}N_2O_5S \cdot HCl$	$C_{19}H_{25}N_5O_4 \cdot HCl \cdot 2H_2O$	$C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$	$C_{19}H_{27}N_5O_4 \cdot HCl$
Molecular weight	444.98	459.93	547.6	425.9
Solubility	Sparingly soluble in water and in methanol; slightly soluble in glacial acetic acid and ethanol; practically insoluble in ether	Freely soluble in water and isotonic saline	Freely soluble in dimethylsulfoxide; soluble in dimethylformamide; slightly soluble in methanol, ethanol, and water (0.8% at 25°C); very slightly soluble in acetone and methylene chloride	Freely soluble in water, sparingly soluble in alcohol, and practically insoluble in dichloromethane
Available formulations and indicated strengths	Capsule for oral administration, each capsule containing 0.4 mg of modified-release tamsulosin HCl	Capsules for oral ingestion in four dosage strengths: 1mg, 2 mg, 5 mg, and 10 mg of terazosin	Colored tablets for oral use in four dosage strengths: 1 mg (white tablets), 2 mg (yellow), 4 mg (orange), and 8 mg (green) of doxazosin	Extended-release tablet for oral administration. 10 mg as a round, three layer tablet: one white layer between two yellow layers
Indications	Indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) **Not** indicated for the treatment of hypertension	Indicated for the treatment of symptomatic BPH Also indicated for the treatment of hypertension, to be used alone or in combination with other antihypertensive agents	Indicated for the treatment of the following symptoms associated with BPH: urinary outflow obstruction and obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning) Also indicated for the treatment of hypertension, used either alone, or in combination with diuretics, beta-adrenergic blocking agents, calcium channel blockers or angiotensin-converting enzyme inhibitors	Indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia **Not** indicated for the treatment of hypertension
Mechanism of action	Selectively blocks the $alpha_{1A}$ adrenoreceptor, which comprises about 70% of $alpha_1$ adrenoreceptors in the human prostate Blockade of $alpha_{1A}$ adrenoreceptors in the prostate, prostatic capsule, prostatic urethra, and bladder neck decreases smooth muscle tone, attenuating the dynamic component of bladder outlet obstruction that causes BPH symptoms	Blockade of alpha-1 adrenoreceptors in the prostate and bladder neck, causing relaxation of smooth muscles, improving urine flow rates and symptoms of BPH Blockade of alpha-1 adrenoreceptors also causes a decrease in blood pressure by decreasing total peripheral vascular resistance	Antagonizes phenylephrine ($alpha_1$ agonist)-induced smooth muscle contractions *in vitro*, and binds with high affinity to subtype $alpha_{1C}$ adrenoreceptors in the prostate Competitively antagonizes the pressor effects of phenylephrine and norepinephrine through selective blockade of the $alpha_1$ (postjunctional) subtype of adrenergic receptors	Blockage of $alpha_1$- adrenergic receptors of the lower urinary tract Blockage of $alpha_1$- adrenergic receptors causes relaxation of smooth muscle in the bladder neck and prostate
Pharmacokinetics				
Absorption	Absorption is almost complete (> 90%) after oral administration under fasting conditions. The time to maximum plasma concentration (T_{max}) is reached by 4 to 5 hours under fasting conditions, and 6 to 7 hours when administered with food. Administration under fasting conditions results in a 30% increase in bioavailability	Absorption is essentially complete. Plasma levels peak after about 1 hour. Food has a minimal effect on the extent of absorption, but the time to reach peak plasma concentration is delayed by about 40 minutes.	Bioavailability is approximately 65%, reflecting first pass metabolism by the liver. Peak plasma levels are reached at about 2-3 hours. Administration with food has been found to result in statistically non-significant reductions of 18% in mean C_{max} and 12% in the AUC. AUC was 11% less after a.m. dosing than after	Absolute bioavailability is 49% under fed conditions. Following multiple dosing under fed conditions, the time to reach maximum concentration is 8 hours. Steady-state plasma levels are reached with the second dose. The extent of absorption is 50% lower under fasting conditions.

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	(AUC) and 40% to 70% increase in peak concentrations (C_{max}) compared to fed conditions. Exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.		p.m. dosing, and after p.m. dosing, C_{max} occurred significantly later than after a.m. dosing (5.6 vs. 3.5 hours).	
Half life	Elimination half-life following IV infusion or oral administration of an immediate release-release formulation is 5-7 hours. Following oral administration of Flomax capsules, the apparent half-life is approximately 9-13 hours in healthy volunteers and 14-15 hours in the target population, due to absorption rate-controlled pharmacokinetics.	Plasma half-life is approximately 12 hours, but depends on age: in patients 20-39 years of age, mean plasma half-life was measured to be 11.4 hours, versus 14.0 hours in patients ≥70 years. After oral administration, plasma clearance was decreased by 31.7% in patients ≥70 years of age compared to patients 20-39 years of age.	Plasma elimination is biphasic, with a terminal elimination half-life of about 22 hours. Steady state studies in hypertensive patients have shown linear kinetics and dose proportionality for doses of 2-16 mg once daily. Secondary peaking of plasma doxazosin suggests enterohepatic cycling.	The apparent elimination half-life is 10 hours following oral administration
Distribution/plasma protein binding	Mean steady-state apparent volume of distribution is 16L after IV administration. Tamsulosin HCL is widely distributed to most tissues; distribution to brain, spinal cord, and testes is minimal. Plasma protein binding is 94-99%, primarily to alpha-1 acid glycoprotein.	Plasma protein binding is 90-94%.	About 98% of circulating doxazosin is plasma protein bound.	The volume of distribution following IV administration was 3.2 L/kg. *In vitro* studies indicate moderate plasma protein binding (82% to 90%), with linear binding over a wide concentration range (5 to 5,000 ng/mL).
Metabolism	There is no enantiometric bioconversion. Extensively metabolized by the liver cytochrome P450 system; the pharmacokinetics of the metabolites has not been established. The metabolites undergo extensive glucuronide or sulfate conjugation prior to urinary excretion. Less than 10% is excreted unchanged in urine.	Nearly all of the circulating dose is in the form of parent drug. Approximately 30% is excreted unchanged (10% in the urine; 20% in the feces); the remainder as metabolites.	Extensively metabolized in the liver, mainly by O-demethylation of the quinazoline nucleus or hydroxylation of the benzodioxam moiety. Several active metabolites have been identified, but their pharmacokinetics has not been established. Only about 4.8% is excreted unchanged (mostly in the feces and a trace in the urine).	Extensively metabolized by the liver, mainly by oxidation, O-demethylation, and N-dealkylation. Metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme involved. 11% of administered dose is excreted unchanged in the urine.
Excretion	Urine is the primary route of excretion, with about 76% of a radiolabeled dose being recovered from urine and 21% from feces over 168 hours. Undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).	Overall, approximately 40% of the administered dose is excreted in the urine, and 60% in the feces.	In a study of two subjects administered radiolabeled doxazosin 2 mg orally and 1 mg intravenously, approximately 63% of the dose was recovered from the feces and 9% was found in the urine.	Following oral administration, the radiolabeled dose being recovered was 69% in feces and 24% in urine
Special populations	Pharmacokinetic disposition may be slightly prolonged in geriatric males with overall exposure (measured as AUC) being 40% higher in subjects 55-75 years of age compared to 20-32 years of age. Patients with mild-moderate and moderate-	Impaired renal function has no significant effect on elimination, and dosage adjustment in patients with renal impairment is not necessary. Pharmacokinetics have not been established in children. Safety and effectiveness in children	Pharmacokinetic studies in elderly patients and patients with renal impairment have shown no significant differences compared to younger patients with normal renal function. In patients with liver cirrhosis, a 40% increase in exposure has been observed.	No relationship between peak plasma concentrations of alfuzosin and age. The concentrations in subjects ≥75 years of age were approximately 35% greater than in those below 65 years of age. Relative to subjects with normal renal function (CL_{CR} >80 mL/min), the mean C_{max} and AUC values

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	severe renal impairment do not require an adjustment in dosing, but patients with endstage renal disease (CL_{CR} < 10 mL/min/1.73m^2 have not been studied. Patients with moderate hepatic dysfunction do not require dosage adjustment. Not indicated for use in women. Not indicated for use in pediatric populations.	have also not been determined.		were increased by approximately 50% in patients with mild (CL_{CR} 60-80 mL/min), moderate (CL_{CR} 30-59 mL/min), or severe renal impairment (CL_{CR} <30 mL/min). Contraindicated in patients with moderate or severe hepatic impairment (Childs-Pugh categories B and C). Pharmacokinetics of alfuzosin has not been studied in patients with mild hepatic insufficiency. Not indicated for use in women. Not indicated for use in children.
Contraindications	Patients with hypersensitivity to the drug or any component of the capsules.	Hypersensitivity to terazosin hydrochloride.	Known sensitivity to quinazolines, doxazosin, or any of the inert ingredients.	In patients with moderate or severe hepatic insufficiency (Childs-Pugh categories B and C). Co-administration with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir. Hypersensitivity to alfuzosin hydrochloride or any component of the tablet.
Warnings	Signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in Flomax than placebo treated patients. Due to a potential risk of syncope, patients beginning treatment should avoid situations where injury could result should syncope occur. Although priapism only rarely occurs (probably less than one in 50,000 patients), patients must be advised about the seriousness of the condition.	Marked lowering of blood pressure, especially postural hypotension, and syncope may occur after the first dose, during the first few days of therapy, or at restarting therapy after an interruption of several days. Also rapid dosage increases, or the introduction of (another) antihypertensive drug might be associated with syncope. To decrease the likelihood of syncope or excessive hypotension, treatment should always be initiated with a 1 mg dose, given at bedtime; dosage should then be increased slowly, and additional antihypertensive agents should be added with caution. Patients should be warned to avoid situations where injury could result from syncope (driving, hazardous tasks). If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary. As rare cases of priapism have been described, patients must be advised about the seriousness of this condition.	Marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness may occur, especially after the first dose, but also when there is a dosage increase, or at restarting therapy after an interruption of more than a few days. To decrease the likelihood of excessive hypotension and syncope, treatment should be initiated with the 1 mg dose; dosage should then be adjusted slowly, with evaluations and dose increases every two weeks to the recommended dose. Additional antihypertensive agents should be added with caution. During this period of titration, patients should be cautioned to avoid situations where injury could result should syncope occur, during both the day and night. If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary. As rare cases of priapism have been described, patients must be advised about the seriousness of this condition.	Within a few hours following administration, postural hypotension with or without symptoms (e.g., dizziness) may develop. There is a potential for syncope. Patients should be warned of possible syncope and should avoid situations where injury could result. Care should be taken with patients with symptomatic hypotension or patients who have had a hypotensive response to other mediations.
General	Prior to initiation of treatment with Flomax, carcinoma of the prostate should be ruled out.	Prior to starting treatment, prostatic cancer should be ruled out. Apart from syncope, other symptoms of lowered blood pressure may occur (dizziness, light-headedness, vertigo, postural hypotension). Patients with occupations in which such events represent potential	Prior to starting treatment, prostatic carcinoma should be ruled out. Other symptoms of lowered blood pressure than syncope, such as dizziness, light-headedness, or vertigo, can also occur. Patients in occupations in which orthostatic hypotension could be dangerous, should be treated with particular	Prior to starting treatment, carcinoma of the prostate should be ruled out. Should not be used in combination with other alpha-blockers. Should be discontinued if symptoms of angina pectoris newly appear or worsen.

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		problems should be treated with caution.	caution.	
Other			Cardura should be administered with caution to patients with evidence of impaired liver function or to patients receiving drugs known to influence hepatic metabolism.	Should not be given to patients with moderate or severe hepatic insufficiency. Pharmacokinetics not studied in patients with mild hepatic insufficiency. Systemic exposure increase by approximately 50% in pharmacokinetic studies of patients with mild, moderate, or severe renal insufficiency. Caution should be exercised in patients with severe renal insufficiency (CL_{CR}< 30 mL/min). In a study of QT effect, the QT effect appeared less with alfuzosin 10 mg than with 40 mg, and the effect if alfuzosin 40 mg did not appear as large as that of the active control moxifloxacin at its therapeutic dose. There as been bo signal of Torsades de Pointe in the extensive post-marketing experience with alfuzosin outside the United States.
Information for Patients	Patients should be told about the possible occurrence of symptoms related to postural hypotension, and they should be cautioned about driving, operating machinery, or performing hazardous tasks. Patients should be advised not to crush, chew or open the capsules. Patients should be advised about the possibility of priapism; they should be informed that this reaction is extremely rare, but if not brought to immediate medical attention can lead to permanent impotence.	Patients should be made aware of the possibility of syncope and orthostatic symptoms. Patients should avoid driving or hazardous tasks for 12 hours after the first dose, after a dosage increase and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result in case of syncope during initiation of therapy; they should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, and to be careful when rising from a sitting or lying position. Patients should be instructed to report symptoms of dizziness, light-headedness or palpitations to their physician when these symptoms are bothersome. Patients should also be told that drowsiness or somnolence can occur, which requires caution in people who must drive or operate machinery. Patients should be advised about the possibility of priapism; they should know that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent impotence.	Patients should be made aware of the possibility of syncope and orthostatic symptoms, especially at the initiation of therapy. Patients should be urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase and after interruption of therapy when treatment is resumed; they should be cautioned to avoid situations where injury could result in case of syncope during initiation of therapy; they should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, and to be careful when rising from a sitting or lying position. Patients should be instructed to report symptoms of dizziness, light-headedness or palpitations to their physician when these symptoms are bothersome. Patients should also be told that drowsiness or somnolence can occur, which requires caution in people who must drive or operate machinery. Patients should be advised about the possibility of priapism; they should know that this reaction is extremely rare, but, if not brought to immediate medical attention, can lead to permanent impotence.	Patients should be told about the possible occurrence of symptoms related to postural hypotension, such as dizziness, when beginning alfuzosin, and they should be cautioned about driving, operating machinery, or performing hazardous taks during this period. Should be taken with food with the same meal each day. Patients should be advised not to crush or chew tablets.
Drug Interactions	Administration of 0.4 and 0.8 mg of Flomax resulted in no clinically significant effects on blood pressure and pulse rate in studies in hypertensive subjects (age 47-79 years)	In controlled trials, terazosin has been added to diuretics, as well as several beta-adrenergic blockers, without any unexpected interactions being observed.	Based on *in vitro* studies, doxazosin has no effect on protein binding of digoxin, warfarin, phenytoin, or indomethacin; there is no information on the effect of other highly plasma	Should not be co-administered with potent inhibitors of CYP3A4 because exposure is increased, (e.g., ketoconazole, itraconazole, or ritonavir).

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	whose blood pressure was controlled with nifedipine, atenolol, or enalapril. Pharmacokinetic and pharmacodynamic interactions with other alpha-adrenergic blocking agents have not been determined, but interactions may be expected. Tamsulosin HCl clearance is significantly reduced (26%) by cimetidine, resulting in a 44% increase in AUC. Interaction studies with warfarin have been inconclusive, therefore caution should be exercised with concomitant administration of warfarin and Flomax. *In vitro* studies indicate that plasma protein binding of tamsulosin HCl is not affected by amitriptyline, diclofenac, glyburide, simvastatin, warfarin, diazepam, propranolol trichlormethiazide, or chlormadinone; likewise, plasma protein binding of these drugs is not affected by tamsulosin HCl.	Without formal interaction studies having been performed, concomitant use with a variety of drugs has resulted in no interactions being observed; these drugs include analgesics, antibiotics, anticholinergic/ sympathomimetics, antigout agents, antihistamines, cardiovascular agents, corticosteroids, gastrointestinal agents, hypoglycemics, and tranquilizers. Verapamil was found to increase the mean AUC_{0-24} of terazosin by 11% after the first verapamil dose and by 24% after 3 weeks of verapamil treatment.	protein bound drugs on doxazosin binding. Administration to patients receiving thiazide diuretics, beta-blocking agents, and NSAIDs has not resulted in adverse drug interactions. In healthy volunteers, doxazosin AUC of doxazosin has been found to be influenced by cimetidine, but the clinical significance of this finding is unknown. Experience exists on concomitant treatment (no formal interactions studies conducted) with analgesics, antibiotics, antihistamines, cardiovascular agents, corticosteroids, gastrointestinal agents, hypoglycemics, sedatives/tranquilizers, and cold and flu remedies; no interactions have been observed.	Although no changes in blood pressure were observed in this study, diltiazem is an antihypertensive medication and the combination of alfuzosin and antihypertensive medications has the potential to cause hypotension in some patients. In human live microsomes, at concentrations that are achieved at the therapeutic dose, alfuzosin did not inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6 or 3A4 isoenzymes. No affect on pharmacological response between alfuzosin and warfarin. No influence on steady-state pharmacokinetics between alfuzosin and digoxin. No evidence of pharmacokinetic or pharmacodynamic interactions between alfuzosin and hydrochlorothiazide. Repeated administration of 1 g/day cimetidine increased both alfuzosin C_{max} and AUC values by 20%. In one study, atenolol increased alfuzosin C_{max} and AUC values by 28% and 21%, respectively. Alfuzosin increased atenolol C_{max} and AUC values by 26% and 14%, respectively. The combination of alfuzosin with atenolol caused significant reductions in mean blood pressure and in mean heart rate.
Drug/Laboratory test interactions	No interactions with laboratory tests are known. Treatment up to 12 months had no effect on PSA.	Small but statistically significant decreases in hematocrit, hemoglobin, white blood cells, total protein, and albumin have been observed in controlled clinical trials, suggesting the possibility of hemodilution. No effect on PSA levels have been identified with terazosin treatment for up to 24 months.	Plasma concentration of PSA remains unaffected for up to 3 years of treatment. Cardura has been associated with decreases in white blood cell counts and neutrophil counts. The risk of leukopenia or neutropenia can not be ruled out.	No laboratory test interactions are known.
Toxicity				
Carcinogenesis	Doses up to 43 mg/kg/day in male rats and 52 mg/kg/day in female rats (AUC 3 times the exposure in men receiving the maximum therapeutic dose of 0.8 mg/day) have shown no increase in tumor incidence with the exception of a modest increase in the frequency of mammary gland fibroadenomas in female rats receiving doses $\geq$5.4 mg/kg ($p<0.015$). Doses up to 127 mg/kg/day in male mice and 158 mg/kg/day in female mice (AUC 8 times the exposure in men receiving the maximum therapeutic dose of 0.8 mg/day)	A statistically significant increase in benign adrenal medullary tumors was observed when male rats were exposed to 250 mg/kg/day doses of terazosin (175 times the maximum recommended human dose [MRHD] of 20 mg/day) for 2 years. Female rats were unaffected. In male and female mice administered terazosin 32 mg/kg/day (9 times the MRHD of 20 mg/day) for 2 years, no evidence of mutagenicity, or increased tumor incidence, has been observed, despite extensive testing.	No evidence of carcinogenic potential has been found upon chronic dietary administration up to 24 months of maximally tolerated doses of 40 mg/kg/day in rats (8 times the human AUC at a dose of 16 mg/day) and 120 mg/kg/day in mice (4 times the human AUC).	No evidence of drug-related increase in the incidence of tumors in mice following dietart administration of 100 mg/kg/day alfuzosin for 98 weeks in females and males, respectively. The highest dose tested in female mice may not have constituted a maximally tolerated dose. Likewise, there is no evidence of a drug-related increase in the incidence of tumors in rats following dietary administration of 100 mg/kg/day alfuzosin for 104 weeks in females and males, respectively.

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	have been administered without significant tumor findings in male mice, but a statistically significant increase in the incidence of mammary gland fibroadenomas ($p<0.0001$) and adenocarcinoma ($p<0.0075$) were seen in female mice after 2 years of treatment. The increased incidences of mammary gland neoplasms in female rats and mice were considered to be secondary to hyperprolactinemia. The relevance of these findings in mice and rats on human risk is unknown as the effect of tamsulosin on prolactin levels in humans is not known.	The increase in benign adrenal medullary adenomas is considered to be a male rat species-specific effect, which does not provide evidence for carcinogenicity in man.		
Mutagenesis	No evidence of mutagenic potential has been found as assessed *in vitro* by the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in Chinese hamster ovary (CHO) cells or human lymphocytes. No mutagenic effects noted in the *in vivo* sister chromatic exchange and mouse micronucleus assays.	No *in vivo* or *in vitro* mutagenesis was observed, as assessed by the Ames test, cytogenetics, the dominant lethal test in mice, CHO cell chromosome aberration test, and V79 forward mutation test.	Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.	No evidence of mutagenic effect in the Ames and mouse lymphoma assays, and was free of any clastogenic effects in the Chinese hamster ovary cell and *in vivo* mouse micronucleus assays. Alfuzosin treatment did not induce DNA repair in a human cell line.
Other toxicities			An increased incidence of myocardial necrosis or fibrosis was found in Sprague-Dawley rats after 6 months of dietary administration of doses calculated to provide 80 mg/kg/day of doxazosin, and 12 months of dietary administration of doses calculated to provide 40 mg/kg/day of doxazosin (about 8 times the human AUC exposure with a 12 mg/day dose). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months (exposure 8 times human AUC exposure in rats and somewhat equivalent to maximum human exposure in mice). No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs at maximum doses of 20 mg/kg/day [14 times the maximum exposure in humans receiving a 12 mg/day dose] and in Wistar rats at doses of 100 mg/kg/day (15 times maximum human exposure with a 12 mg/day dose). There is no evidence that similar lesions occur in humans.	No evidence of reproductive organ toxicity when male rats were given alfuzosin at daily oral (gavage) doses of up to 250 mg/kg/day for 26 weeks. No impairment of fertility was observed following oral (gavage) administration to male rats at doses of up to 125 mg/kg/day for 70 days.
Effects on fertility	Doses of tamsulosin 300 mg/kg/day administered to male rats (AUC of 50 times the human exposure with maximum therapeutic dose of 0.8mg/day) revealed significantly reduced fertility, which was	Testicular weights and morphology of male rats were unaffected by terazosin treatment with doses of 30 and 120 mg/kg/day (20 and 80 times the MRHD, respectively). But reduced sperm counts were recovered from	Reduced fertility was found in male rats treated with oral doses of about 4 times the human AUC exposure with a 12 mg/day dose, but not at lower dosages. This effect was reversible within 2 weeks of drug withdrawal.	Estrous cycling was inhibited in rats and dogs at doses of 25 mg/kg and 20 mg/kg, respectively, corresponding to levels of systemic exposure 12- and 18-fold higher, respectively, than in humans, although this did not result in impaired fertility in

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	reversible after dose reduction or discontinuation. The mechanism for decreased fertility was considered to be an effect on vaginal plug formation possibly due to changes of semen content or impairment of ejaculation. Effects of tamsulosin on sperm count or function have not been evaluated. In female rats, significant reductions in fertility were observed at doses of 300 mg/kg/day, which were considered to be associated with impairments in fertilization.	vaginal smears of female rats compared to control matings, which seemed to correlate with subsequent reductions in the rates of pregnancy. A statistically insignificant increase in the incidence of testicular atrophy was found in male rats exposed to terazosin doses of 40 and 250 mg/kg/day (29 and 175 times the MRHD, respectively) for up to 2 years. Testicular atrophy was also observed in dogs dosed with 300 mg/kg/day (>500 times the MRHD) for 3 months, but not after 1 year of treatment with 20 mg/kg/day (38 times the MRHD).	There have been no reports of effects on fertility in humans.	rats.
Pregnancy Category	B Doses of up to 300 mg/kg/day administered to pregnant female rats (approximately 50 times the human therapeutic AUC exposure) produced no evidence of fetal harm. Doses of up to 50 mg/kg/day administered to pregnant female rabbits produced no evidence of fetal harm.	C The safety in human pregnancy has not been established, as no well-controlled studies in pregnant women have been performed. No teratogenic effects were observed in either rats or rabbits when oral doses up to 280 and 60 times the MRHD, respectively were administered. Fetal resorptions occurred in rats dosed with 280 times the MRHD. In rabbits dosed with 60 times the MRHD, increased fetal resorptions, decreased fetal weight, and an increased number of supernumerary ribs in offspring were observed.	C No studies in pregnant women have been performed. Studies in pregnant rabbits and rats with doses up to 10 and 4 times human AUC exposures with a 12 mg/day therapeutic dose, respectively have revealed no evidence of harm to the fetus. A dosage of 82 mg/kg/day in the rabbit (20 times human AUC exposure) was associated with reduced fetal survival. Following oral administration of radiolabeled doxazosin to pregnant rats, radioactivity was found to cross the placenta.	B No evidence of tertatogenicity or embryotoxicity in rats at maternal (oral gavage) doses up to 250 mg/kg/day, corresponding to systemic exposure levels 1,200-fold higher than in humans. In rabbits, up to the dose of 100 mg/kg/day given orally (via gavage), no evidence of fetal toxicity or teratogenicity was seen. Gestation was slightly prolonged in rats with a maternal dose >5 mg/kg/day (oral gavage). There were no difficulties with parturition.
Safety experience	Safety has been evaluated in 1783 patients treated with daily doses of 0.1 to 0.8 mg capsules (compared with 798 patients treated with placebo) in six short-term US and European clinical trials. Post-marketing experience is also available.	For the indication BPH, the safety and efficacy of terazosin have been evaluated in 6 worldwide placebo-controlled trials involving 636 patients treated with doses of terazosin ranging from 1 to 20 mg, versus a total of 360 patients in the control groups. The safety profile of patients treated in a long-term open-label study was similar to that observed in the controlled studies. For the indication hypertension, terazosin has been evaluated in clinical trials conducted primarily in the US, at doses ranging from 1 to 40 mg, and including a total of 859 patients in the treatment groups versus 506 patients in the control groups. Post-marketing experience is also available.	For the indication BPH, efficacy and safety of Cardura have been studied in worldwide clinical trials involving 965 normotensive BPH patients, 665 treated with doses of doxazosin ranging from 0.5 to 8mg for a mean of 85 days, versus 300 in the placebo groups. For the indication hypertension, Cardura has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program, at doses ranging from 1 to 16 mg. The safety and effectiveness profiles have been found to be similar in the elderly (≥65 years) and younger (< 65 years).	Safety was evaluated in 3 placebo-controlled clinical trials involving 1,608 (473 mean received alfuzosin HCl 10 mg extended-release tablets) men with daily doses of 10 and 15 mg alfuzosin. In general, the adverse events seen in long-term use were similair in type and frequency to the events for the 3-month trials.
Adverse	Treatment-emergent adverse events with	When administered for the BPH or for	The BPH indication:	The treatment-emergent adverse events occurring in

	Flomax® (tamsulosin hydrochloride)	Hytrin® (terazosin hydrochloride)	Cardura® (doxazosin mesylate)	Uroxatral™ (alfuzosin hydrochloride)
reactions/events	≥2% incidence in patients treated with either 0.4 or 0.8 mg Flomax during two 13-week US trials conducted in 1487 men were headache, infection, asthenia, back pain, chest pain, dizziness, somnolence, insomnia, decreased libido, rhinitis, pharyngitis, increased cough, sinusitis, diarrhea, nausea, tooth disorders, abnormal ejaculation, and amblyopia. Signs and symptoms of orthostasis included: postural hypotension, syncope, dizziness, and vertigo. Multiple testing for orthostatic hypotension was conducted; overall, symptoms were detected more frequently in the treatment groups than in the placebo groups, hence it was concluded there is a potential risk of syncope. Abnormal ejaculation (ejaculation failure, ejaculation disorder, retrograde ejaculation, ejaculation decrease) was associated with Flomax administration and was dose-related. Allergic-type reactions have been reported in post-marketing experience. Priapism has been reported rarely during the post-marketing period. Infrequent reports of palpitations, constipation and vomiting have been received during the post-marketing period.	hypertension, the only events that were significantly more common ($p \leq 0.05$) in patients receiving terazosin were: Asthenia Blurred vision (HTN indication only) Postural hypotension (only BPH indication), which a separate analysis showed to be associated with a risk greatest during the initial 7 days of treatment, but which continued at all time intervals. Dizziness Somnolence Nasal congestion/rhinitis Nausea (HTN only) Impotence (BPH only) Peripheral edema (HTN only) Palpitations (HTN only) Adverse events were usually transient and mild or moderate in intensity, but in some cases were serious enough to interrupt treatment. The incidence of urinary tract infection was significantly lower in terazosin treated patients (BPH indication). Post-marketing experience indicates that in rare instances patients may develop allergic reactions, including anaphylaxis. There have also been reports of priapism, thrombocytopenia, and atrial fibrillation.	Adverse events that were significantly more common in the treatment groups than in the placebo groups of the controlled clinical trials were: Dizziness (dose-related) Fatigue Hypotension Edema Dyspnea (dose-related) HTN Indication: In the clinical development program, minor adverse events were frequent, but led to discontinuation of treatment in only 7% of patients. Adverse events that were significantly more frequent in the treatment groups were: Dizziness Weight gain Somnolence Fatigue/malaise Postural effects and edema appeared to be related.	≥2% of alfuzosin HCl extended release- treated patients (N= 473) in 3-month placebo-controlled clinical studies were dizziness, upper respiratory tract infection, headache, and fatigue. Symptoms possibly associated with orthostasis in 3-month placebo-controlled clinical studies with alfuzosin 10 mg include dizziness, hypotension or postural hypotension, and syncope. Multiple testing for blood pressure changes or orthostatic hypotension was conducted in three controlled studies. Decreased systolic blood pressure was observed in none of the 674 placebo patients and 1 (0.2%) of the 469 alfuzosin patients. Decreased diastolic blood pressure was observed in 3 (0.4%) of the placebo patients and in 4 (0.9%) of the alfuzosin patients. A positive orthostatic test was seen in 52 (7.7%) of placebo patients and in 31 (6.6%) of the alfuzosin patients. Adverse events reported in post-marketing experience include: rash, tachycardia, chest pain, and priapism.
Dosage and administration	The recommended dose is 0.4 mg once daily, to be administered one-half hour following the same meal each day. If patients do not respond to this dose after 2 to 4 weeks of treatment, the dose can be increased to 0.8 mg once daily. If treatment is discontinued or interrupted for several days, therapy should be restarted with the 0.4 mg daily dose.	The recommended initial dose is 1 mg at bedtime for all patients. The dose should then be increased in a stepwise fashion to 2 mg, 5 mg, or 10 mg once daily to achieve the desired improvement of symptoms. Doses of 10 mg are generally required for clinical response, and should be given for a period of at least 4-6 weeks to assess whether a beneficial response has been achieved. After interruption of therapy for several day or longer, therapy should be re-instituted at the initial dosing regimen.	Dosage must be individualized. The initial dosage for BPH is 1 mg given once daily a.m. or p.m. Depending on the individual patient's urodynamics and symptomatology, dosage may then be increased to 2 mg and thereafter to 4 mg and 8 mg once daily. The recommended titration interval is 1-2 weeks. After the first dose and with each increase in dosage, blood pressure measurements should be taken between 2 and 6 hours after the dose.	The recommended dosage in one 10 mg alfuzosin HCl extended-release tablet daily to be taken immediately after the same meal each day.

	Proscar® (finasteride)	Avodart® (dutasteride)
Empirical formula	$C_{23}H_{36}N_2O_2$	$C_{27}H_{30}F_6N_2O_2$
Molecular weight	372.55	528.5
Solubility	Freely soluble in chloroform and in lower alcohol solvents; practically insoluble in water	Soluble in ethanol, methanol, and polyethylene glycol 400; insoluble in water
Available formulations and indicated strengths	Film-coated tablets for oral administration, each tablet containing 5 mg of finasteride	Soft gelatin capsules for oral administration, each capsule containing 0.5 mg of dutasteride
Indications	Indicated for the treatment of symptomatic BPH in men with an enlarged prostrate to improve symptoms, reduce the risk of acute urinary retention and decrease the need for surgery including TURP and prostatectomy	Indicated for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery
Mechanism of action	Specifically and competitively inhibits Type II 5(alpha)-reductase, an intracellular enzyme that converts testosterone into 5(alpha)-dihydrotestosterone, the active androgen that drives the enlargement of the prostate by binding to androgen receptors in the nuclei of prostatic cells. Inhibits Type II 5(alpha)-reductase by slowly forming a stable enzyme complex with it; turnover from this complex is extremely slow ($t_{½}$ ~ 30 days).	Inhibits the conversion of testosterone to 5(alpha)-dihydrotestosterone, the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Specifically and competitively inhibits both Type I (active in the skin and liver) and Type II (active in reproductive tissues) 5(alpha)-reductase isoenzymes by forming a stable enzyme complex; dissociation from this complex is extremely slow.
Pharmacokinetics		
Absorption	Mean bioavailability is 63% (range 34-108%) when measured as the ratio of the AUC to an IV reference dose. C_{max} averaged 37 ng/mL (27-49 ng/mL) and was reached after 1-2 hours. Bioavailability is not affected by food.	Absolute bioavailability is approximately 60% (range 40-94%). T_{max} occurs within 2-3 hours. Steady-state serum concentration averaged 40 ng/mL following 0.5 mg/day dosing for 1 year. Following daily dosing for 1 month and 3 months, 65% and 90% of steady-state serum dutasteride concentration was achieved, respectively. C_{max} is reduced by 10-15% when the drug is administered with food, but this reduction is not clinically significant.
Half life	Mean elimination half-life in plasma was 6 hours (range, 3-16 hours) in healthy young subjects. Mean terminal half-life was 6 hours (4-12 hours) in subjects 45-60 years, and 8 hours (6-15 hours) in subjects ≥70 years.	The terminal elimination half-life is ~ 5 weeks at steady state. Due to the long half-life, serum concentrations remain detectable (> 0.1 ng/mL) for up to 4-6 months after treatment discontinuation.
Distribution/plasma protein binding	Mean steady-state volume of distribution is 76L (range 44-96L). Approximately 90% of circulating drug is bound to plasma proteins. Crosses the blood brain barrier but does not appear to distribute preferentially to cerebrospinal fluid.	Following single and repeated oral doses the volume of distribution is 300-500L. Dutasteride is highly bound to plasma albumin (99.0%) and alpha-1 acid glycoprotein (96.6%). Approximately 11.5% of serum dutasteride concentrations partition into semen at 12 months.
Metabolism	Extensively metabolized in the liver, primarily via the cytochrome P450 3A4 pathway. Two metabolites have been identified (a t-butyl side chain mono-hydroxylated and a mono-carboxylic acid metabolite), which possess no more than 20% of the 5(alpha)-reductase inhibitory activity of finasteride.	In vitro, dutasteride is extensively metabolized by the cytochrome P450 3A4 isoenzyme to 2 minor mono-hydrate metabolites. In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4´-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydoxydutasteride) and 2 minor metabolites (6, 4´-dihydroxydutasteride and 15- hydroxy-dutasteride) have been detected.
Excretion	In healthy subjects, mean plasma clearance was 165 mL/min (range 70-279L). A mean of 39% (32-46%) is excreted in the urine as metabolites; 57% (51-64%) is excreted in the feces.	Excreted mainly in feces as ~ 5% unchanged dutasteride (~1-15%) and 40% as dutasteride-related metabolites (~2-90%). Trace amounts of unchanged dutasteride are found in urine (<1%).

	Proscar® (finasteride)	Avodart® (dutasteride)
Special populations	Elimination rate of finasteride in the elderly is decreased (AUC 15% higher in subjects > 70 years than in subjects 45-60 years of age), however, no dosage adjustment is necessary. No dosage adjustment is required in patients with renal insufficiency. The effect of hepatic insufficiency has not been studied. Data in women is not available. Pharmacokinetics have not been investigated in subjects < 18 years of age. The effect of race has not been studied.	Half-life of dutasteride increased with age (~ 170 hours in men 20-49 years of age, ~ 260 hours in men 50-69 years of age, and ~ 300 hours in men > 70 tears of age), however no dosage adjustment is necessary. The effect of renal impairment on dutasteride pharmacokinetics has not been studied; however, no dosage adjustment is anticipated in patients with renal impairment. Data in women is not available. Pharmacokinetics have not been investigated in subjects < 18 years of age. The effect of race has not been studied.
Contraindications	Hypersensitivity to any component of the formulation. Pregnancy or women when they may potentially be pregnant.	Hypersensitivity to dutasteride, other 5(alpha)-reductase inhibitors, or any component of the preparation. Not for use in women or children.
Warnings	Women should not handle crushed or broken Proscar tablets when they are pregnant or may be potentially pregnant.	Women who are or may be pregnant should not handle Avodart because of the possibility of absorption of dutasteride through the skin and the potential risk of fetal anomaly to a male fetus.
Precautions		
General	Prior to initiating therapy, other conditions that might mimic BPH should be ruled out. Patients with large residual urinary volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy, as these patients may not be candidates for finasteride therapy. Caution should be exercised in patients with liver function abnormalities.	Prior to initiating therapy, other conditions that might mimic BPH should be ruled out. Patients with large residual urinary volume and/or severely diminished urinary flow may not be good candidates for 5(alpha)-reductase inhibitor therapy and should be carefully monitored for obstructive uropathy. Caution should be exercised in patients with liver function abnormalities. Blood donation should be avoided until at least 6 months have passed following the last dose of dutasteride to prevent administration of dutasteride to pregnant female transfusion recipients.
Other	No clinical benefit has been demonstrated in patients with prostate cancer, even though Prostate Specific Antigen (PSA) levels may decrease by 50% as a result of treatment. During treatment with Proscar, PSA values should be doubled to preserve sensitivity and specificity of PSA assays in detecting prostate cancer under treatment. However, when using percent free PSA, this is not necessary. Any sustained increases in PSA levels while on treatment should be carefully evaluated, including consideration of non-compliance.	Dutasteride reduces total serum PSA concentrations ~ 40% following 3 months of treatment and ~ 50% following 6, 12, and 24 months of treatment. New baseline PSA concentrations should be established after 3-6 months of treatment for use in assessing potentially cancer-related changes in PSA. To interpret an isolated PSA value in a man treated for $\geq$ 6 months, the PSA value should be doubled for comparison with normal values in untreated men.
Information for Patients	Women should be warned not to handle crushed or broken tablets when they are pregnant or may potentially be pregnant. Physicians should warn the patients that the volume of the ejaculate may be decreased in some patients, but that this decrease does not seem to interfere with normal sexual function. Impotence and decreased libido may occur. Physicians should instruct their patients to read the patient	Women who are or may be pregnant should not handle Avodart because of the potential for absorption through the skin and the subsequent risk of fetal anomaly to a developing male fetus. Physicians should inform patients that ejaculate volume may be decreased in some patients, but that this decrease does not seem to interfere with normal sexual function. Impotence and decreased libido may occur. Physicians should instruct their patients to read the patient

	Proscar® (finasteride)	Avodart® (dutasteride)
	package insert before starting therapy, and to reread it each time the prescription is renewed.	package insert before starting therapy, and to reread it each time the prescription is renewed. Blood donation should be avoided for at least 6 months after the last dose of dutasteride to prevent pregnant women from receiving dutasteride through blood transfusion.
Drug Interactions	No drug interactions of clinical importance have been identified. Compounds that have been tested in men include antipyrine, digoxin, propranolol, theophylline, and warfarin. Without specific interaction studies having been performed, finasteride has been concomitantly used in clinical studies with acetaminophen, acetylsalicylic acid, α_1-receptor antagonists, ACE inhibitors, analgesics, anti-convulsants, beta-adrenergic blocking agents, diuretics, calcium channel blockers, cardiac nitrates, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, H_2 antagonists, and quinolonones, all without evidence of clinically significant adverse reactions.	Dutasteride does not inhibit the in vitro metabolism of model substrates for the major cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1000 ng/mL (> 25 times the steady state serum concentration in humans); however, care should be taken when administering dutasteride with potent, chronic CYP3A4 inhibitors (e.g. verapamil, diltiazem). No alteration in steady state pharmacokinetics of digoxin resulted after concomitant administration for 3 weeks. No alteration in steady state pharmacokinetics of S- or R-warfarin isomers or alteration in the effect of warfarin on prothrombin time occurred after concomitant administration for 3 weeks. No effect on the steady state pharmacokinetics of tamsulosin or terazosin was observed during concomitant administration in a single sequence, cross-over study in healthy volunteers. The relative bioavailability of dutasteride was unaffected by administration 1 hour following a dose of cholestyramine 12 g. Although specific interaction studies were not performed with other compounds, ~ 90% of subjects in Phase III pivotal efficacy studies were taking other medications concomitantly with Avodart. No clinically significant adverse interactions could be attributed to the combination of Avodart and concurrent therapy with anti-hyperlipidemics, angiotensin converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory agents (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.
Drug/Laboratory test interactions	No effect has been found on circulating levels of cortisol, estradiol, prolactin, thyroid-stimulating hormone, or thyroxine. No clinically meaningful effect was observed on the plasma lipid profile or bone mineral density. Increases of about 10% were observed in leuteinizing hormone (LH) and follicle-stimulating hormone (FSH), but levels remained within the normal range. The response of LH and FSH to gonadotropin-releasing hormone remained unaltered in healthy volunteers. No clinically meaningful effects on sperm concentration, mobility, morphology, or pH were found in healthy male volunteers treated with Proscar for 24 weeks, but a 0.6 mL (22.1%) median decrease in ejaculate volume with a concomitant reduction in total sperm per ejaculate was observed. These parameters remained within the normal range and returned to baseline within 84 weeks after therapy discontinuation.	PSA levels decrease in patients treated with Avodart as prostate volume decreases. A 20% decrease in PSA is seen within the 1st month of therapy ; after 6 months PSA levels stabilize at a new baseline ~ 50% of the pre-treatment value. No clinically significant change in sex hormone binding globulin, estradiol, luteinizing hormone, follicle-stimulating hormone, thyroxine (free T4), and dehydroepiandrosterone was seen following 52 weeks of therapy with dutasteride 0.5 mg/day in healthy volunteers. Statistically significant increases in total testosterone and thyroid-stimulating hormone (TSH) were observed at 8 weeks and 52 weeks respectively, in healthy volunteers. Mean levels of testosterone and TSH returned to baseline 24 weeks post-treatment. In BPH patients, a median % increase in luteinizing hormone of 12% at 6 months, and 19% at 12 and 24 months was observed in dutasteride-treated patients.

	Proscar® (finasteride)	Avodart® (dutasteride)
Toxicity		
Carcinogenesis	No evidence of tumorigenesis was observed in a 24-month study in rats receiving doses of up to 160 mg/kg/day in males and 320 mg/kg /day in females (exposures of 111 and 274 times, respectively the recommended human dose of 5 mg/day). In a 19-month carcinogenicity study in mice, a statistically significant ($p \leq 0.05$) increase in the incidence of Leydig cell adenomas was observed at a dose of 228 times the human exposure. At a dose of 23 times the human exposure (mice) and 39 times the human exposure (rats), respectively, an increase in Leydig cell hyperplasia was observed, which correlates with an increase in serum LH levels. No drug-related Leydig cell changes were seen in rats (at 30 times the human exposure) or dogs (at 350 times the human exposure) treated with finasteride for 1 year.	An increased incidence of benign hepatocellular adenomas was noted in a 2-year study in B6C3F1 female mice exposed to 250 mg/kg/day (290 times the expected clinical exposure of 0.5 mg/day in humans). No evidence of carcinogenesis was observed at doses of 3, 35, 250, and 500 mg/kg/day for males or 3 and 35 mg/kg/day for females. In a 2-year study in Han Wistar rats, an increase in Leydig cell adenomas in the testes of male rats was observed at 53 mg/kg/day (135 times the expected clinical exposure in humans). An increase in Leydig cell hyperplasia was present at 7.5 mg/kg/day (52 times the expected clinical exposure in humans) and 53 mg/kg/day in male rats. At tumorigenic doses, luteinizing hormone levels were increased by 167%.
Mutagenesis	No evidence for mutagenicity was found in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay in CHO cells, a slight increase in chromosome aberrations was observed, which corresponded to 4000-5000 times the peak plasma levels in man given a total dose of 5 mg. In an *in vivo* chromosome aberration assay in mice, no increase in chromosome aberration was observed up to a dose of 228 times the human exposure.	A bacterial mutagenesis assay (Ames test), a chromosomal aberration assay in CHO cells, and a micronucleus assay in rats demonstrated no evidence of genotoxicity for the parent drug. The Ames test or an abbreviated Ames test were also negative for the two major human metabolites of dutasteride.
Other toxicities		
Effects on fertility	No effect on fertility, sperm count, or ejaculate volume was seen in sexually mature male rabbits treated with 80 mg/kg/day (543 times the human exposure) for up to 12 weeks. In sexually mature male rats treated with 80 mg/kg/day (61 times the human exposure) no significant effects on fertility were found at 6 and 12 weeks of treatment, but after 24 and 30 weeks there was an apparent decrease in fertility, fecundity and an associated significant decrease in the weights of the seminal vesicles and prostates. The decrease in fertility is secondary to the effect on accessory sex organs, resulting in failure to form a seminal plug, which is not relevant in man. All of these effects were reversible within 6 weeks of treatment discontinuation. No effect on testes or on mating performance has been observed in rats or rabbits.	Treatment of sexually mature rats with 0.05, 10, 50 and 500 mg/kg/day (0.1 to 110 times the expected clinical exposure in humans) for up to 31 weeks resulted in dose- and time-dependent reductions in fertility, reduced cauda epididymal (absolute) sperm counts but not sperm concentration (at 50 and 500 mg/kg/day), reduced weights of the epididymis, prostate and seminal vesicles, an microscopic changes in the male reproductive organs. Fertility effects were reversed by recovery week 6 at all doses, and sperm counts were normal at the end of a 14-week recovery period. Microscopic changes were no longer present at recovery week 14 in the low-dose group and were partly recovered in the remaining treatment groups. Low levels of dutasteride (0.6-17 ng/mL) were detected in the serum of untreated female rats mated to males dosed at 10, 50 and 500 mg/kg/day for 29-30 weeks. Oral administration of 0.05, 2.5, 12.5 and 30 mg/kg/day to female rats resulted in reduced litter size, increased embryo resorption and feminization of male fetuses (decreased anogenital distance) at doses of $\geq$ 2.5 mg/kg/day (2-10 times the expected clinical exposure in human males). Fetal body weights were also reduced at $\geq$ 0.05 mg/kg/day (< 2 times the expected clinical exposure in humans).
Central Nervous System (CNS)		In rats and dogs, repeated oral administration resulted in non-specific, reversible, centrally-mediated toxicity, without associated histopathological changes at exposures 425 and 315

	Proscar® (finasteride)	Avodart® (dutasteride)
		times the expected clinical exposure in humans, respectively.
Pregnancy Category	X Doses of 1-1000 times the recommended human dose to pregnant rats resulted in dose-dependent hypospadias in 3.6 to 100% of male offspring. Also other fetal malformations have been observed in rats and other animals, as to be expected regarding the mechanism of action of the drug. No developmental disorders have been observed in F_1 generation male or female offspring resulting from mating treated male rats (at 80 mg/kg/day, 61 times the human exposure) with untreated female rats. A rhesus monkey model was used to study the risk to the fetus of exposure of pregnant women to finasteride in the semen of men. IV doses of 60 to 120 times the highest estimated human exposure did not result in fetal abnormalities, but doses of 1-2 million times the highest exposure did result in external genital abnormalities in male fetuses.	X IV doses of 400, 780, 1325 or 2010 ng/day (32-186 times the potential maximum exposure of a human female) administered to rhesus monkey embryos on gestation days 20-100 did not adversely affect development of male external genitalia, however, reduction of fetal adrenal and prostate weights and increases in fetal ovarian and testis weights were observed in monkeys treated with the highest doses. Oral administration of 0.05, 2.5, 12.5, and 30 mg/kg/day (0.07-111 times the expected male clinical exposure) to pregnant female rats resulted in feminization of male fetuses (decreased anogenital distance) and male offspring (nipple development, hypospadias, and distended preputial glands) at all doses. An increase in stillborn pups was observed at 30 mg/kg/day, and reduced fetal body weight was observed at doses $\geq$ 2.5 mg/kg/day (15-111 times the expected clinical exposure). Increased incidences of skeletal variations considered to be delays in ossification associated with reduced body weight were observed at doses of 12.5 and 30 mg/kg/day (56-111 times the expected clinical exposure). In an oral pre- an post-natal development study in rats, unequivocal evidence of feminization of the genitalia (decreased anogenital distance, increased incidence of hypospadias, nipple development) of F1 generation male offspring occurred at doses $\geq$ 2.5 mg/kg/day (14-90 times the expected clinical exposure in men). At daily doses of 0.05 mg/kg/day (0.05 times the expected clinical exposure), evidence of feminization was limited to a small, but statistically significant, decrease in anogenital distance. Doses of 2.5-30 mg/kg/day resulted in prolonged gestation in the parental females, a decrease in time to vaginal patency for female offspring, and a decrease in prostate and seminal vesicle weights in male offspring. Effects on newborn startle response were noted at doses $\geq$ 12.5 mg/kg/day. Increased stillbirths were noted at 30 mg/kg/day. Oral administration of 0.05, 0.4, 3.0, 30, 100 and 200 mg/kg doses (0.3-93 times the expected clinical exposure in men) on days 7-29 of pregnant rabbits, revealed evidence of feminization of the genitalia of male fetuses at all doses.
Safety experience	In a long-term efficacy and safety study, 1524 patients treated with Proscar and 1516 patients treated with placebo have been followed over a period of 4 years. This study has been extended into a 5-year open extension study.	In Phase III studies, 2167 male subjects, 47-94 years of age (mean age 66 years), with BPH have been treated with Avodart; 1772 subjects were treated for 1year and 1510 subjects were treated for 2 years.
Adverse reactions/events	Generally, Proscar is well tolerated and adverse reactions usually have been mild and transient. The most frequently reported adverse reactions were related to sexual function, including impotence, decreased libido, decreased volume of ejaculate, and ejaculation disorders. In years 2-4 of the study there was no significant difference between the treatment groups in incidences of impotence, decreased libido and ejaculation disorder. Other adverse reactions reported include breast enlargement,	Most adverse reactions were mild or moderate and generally resolved while on treatment. The most common adverse events leading to withdrawal were associated with the reproductive system, including impotence, decreased libido, ejaculation disorders, and gynecomastia (including breast tenderness and breast enlargement). The incidence of most drug-related sexual adverse events (impotence, decreased libido and ejaculation disorders) decreased with duration of treatment. The incidence of gynecomastia remained constant over the period. The

	Proscar® (finasteride)	Avodart® (dutasteride)
	breast tenderness and rash. In post-marketing experience, hypersensitivity reactions and testicular pain have been reported.	relationship between long-term use of dutasteride and breast neoplasia is currently unknown.
Dosage and administration	The recommended dose is 5 mg orally once a day, to be administered with or without meals.	The recommended dose is 0.5 mg orally once a day, to be administered with or without meals. The capsules should be swallowed whole.

2.2 Place of product in therapy

2.2.a Epidemiology and risk factors

It is common for the prostate gland to become enlarged as a man ages; this condition is known as benign prostatic hyperplasia (BPH). This enlargement doesn't usually cause problems until late in life – BPH rarely causes symptoms before age 40, but more than half of men in their sixties and as many as 90% in their seventies and eighties have some symptoms of BPH.[1] Symptomatic BPH is characterized by lower urinary tract symptoms (LUTS) associated with benign prostatic obstruction (BPO). Approximately 26% of men aged 40-49 years have moderate to severe LUTS – this increases to 46% of men in their seventies.[2] In addition, 10% of men with BPH develop acute urinary retention. In terms of the impact of BPH on healthcare resource use, in the U.S. alone there are 375,000 hospital stays each year that involve a diagnosis of BPH[1]; and 1.7 million men visit the doctor each year due to BPH.[3] As the US population ages, the incidence of BPH and associated costs will continue to grow.

Age and normal male androgenic function are the two most well-established risk factors for BPH.[4] It is not clear whether certain groups face a greater risk of getting BPH. Studies done over the years suggest that BPH occurs more often among married men than single men and is more common in the U.S. and Europe than in other parts of the world. However, these findings have been debated, and no definite information on risk factors exists.[1]

2.2.b Pathophysiology

The underlying cause of BPH has not been clearly identified, although there are a number of possible theories.[1,4] Animal studies have suggested a possible link between the occurrence of BPH and a reduction in the levels of testosterone (versus the female hormone estrogen) in the blood. As men age, the amount of active testosterone in the blood decreases, and the relatively higher amount of estrogen within the prostate gland can lead to increased activity of substances that promote cell growth. Other theories focus on increased levels of dihydrotestosterone (DHT) in the prostate, or genetic "instructions" given to certain prostate cells early in life.[1]

LUTS can occur due to the simple mechanical obstruction associated with BPO, with the increased prostatic mass compressing the urethra and inhibiting urinary flow. However, LUTS suggestive of BPO can also arise through the dynamic component of the sympathetic tone of the smooth muscle in the prostate gland.[5] The contraction of prostate and urethral smooth muscle is mediated by α-adrenergic receptors. There are several types of α-receptors and they are present in varying amounts at the bladder neck, prostatic urethra, capsule and prostatic stroma. It has been shown that the α_{1A}-adrenoceptor is primarily present and responsible for the contraction of smooth muscle of the prostate.[6] Recent evidence also indicates that the presence of α_{1D}-adrenergic receptors in human bladder and spinal cord may play a role in the pathophysiology of prostatic disease.[7]

2.2.c Clinical presentation and diagnosis

The most common symptoms of BPH involve changes or problems with urination[1], including:

- a hesitant, interrupted, weak stream

- urgency and leaking or dribbling
- more frequent urination, especially at night

The size of the prostate does not always determine how severe the obstruction or the symptoms will be. Some men with greatly enlarged glands have little obstruction and few symptoms while others with smaller glands have more blockage and many symptoms. In certain cases, men will suddenly find themselves unable to urinate at all, a condition known as acute urinary retention.

The diagnosis of BPH may involve one or more of the following tests:

1. **Digital Rectal Exam (DRE) –** The DRE is usually the first test that is performed on new patients with symptoms suggestive of BPH. A doctor will insert a gloved finger into the rectum and feel the part of the prostate next to the rectum in order to get a general idea of the size and condition of the gland.

2. **Prostate Specific Antigen (PSA) Blood Test –** PSA, a protein produced by prostate cells, is frequently present at elevated levels in the blood of men who have prostate cancer. In 1997 92% of urologists reported using PSA blood tests in the routine diagnostic work-up of patients with urinary symptoms related to BPH for differentiating BPH from prostate cancer.[8] However, much remains unknown about the interpretation of PSA levels, and PSA blood tests are known to have relatively high false-positive rates.[1]

3. **Rectal Ultrasound –** In this procedure, a probe inserted in the rectum directs sound waves at the prostate – the echo patterns of the sound waves form an image of the prostate gland on a display screen.

4. **Urine Flow Study –** Patients will urinate into a special device that measures how quickly the urine is flowing – reduced flow often suggests BPH.

5. **Intravenous Pyelogram (IVP) –** In this test, a dye is injected into a vein in the urinary tract and an x-ray is taken. The dye makes the urine visible on the x-ray and shows any obstruction or blockage in the urinary tract.

6. **Cystoscopy –** In this exam, the doctor inserts a small tube through the opening of the urethra in the penis. The tube contains a lens and light system that allows the doctor to determine the size of the prostate gland and identify the location and degree of any obstruction.

2.2.d Approaches to treatment

In the U.S., patterns of treatment for BPH are evolving, with movement from primarily surgical treatment (open prostatectomy and transurethral resection of the prostate [TURP], as well as newer, less invasive options like transurethral microwave thermotherapy [TUMT] and transurethral needle ablation [TUNA] of the prostate)) toward medical management of BPH symptoms.[9,10] There are two main categories of medical therapy for BPH. The first includes the long-acting α_1-adrenoceptor antagonists, including Flomax®, doxazosin and terazosin. These drugs act by relaxing the smooth muscle of the prostate and bladder neck to improve urine flow

and to reduce bladder outlet obstruction. Currently, α_1-adrenoceptor antagonists as a class are the most commonly used first-line drugs in the management of symptomatic BPH – approximately 80% of BPH patients receiving medical management are prescribed α_1-adrenoceptor antagonists.[11] The second category comprises the 5α-reductase inhibitor finasteride, which inhibits the production of DTH, which is involved with prostate enlargement. Recent evidence has indicated that finasteride should ideally be used in patients with prostate glands over 40 grams in size.[12]

The main concern when using long-acting α_1-adrenoceptor antagonists is the incidence of systemic side effects, particularly cardiovascular side effects, which manifest as postural hypotension, dizziness, syncope and fatigue. There are important differences among the α_1-adrenoceptor antagonists in this regard. Doxazosin and terazosin were developed first to treat high blood pressure, and are not selective inhibitors of α_1-adrenoceptors. These two drugs have been associated with a statistically significantly greater incidence of systemic side effects than placebo, including dizziness and orthostatic hypotension.[13] In addition, dose titration is required to reduce the occurrence of symptomatic hypotension.

Flomax® is the first selective α_{1A}-adrenoceptor antagonist developed specifically to treat BPH, and has a 7- to 38-fold greater selectivity for the cloned α_{1A}- than the cloned α_{1B}- adrenoceptor, which has been associated with a reduction in peripheral vascular resistance, orthostatic hypotension and associated symptoms such as dizziness.[14,15] In contrast to doxazosin and terazosin, Flomax® does not require titration as patients can be started with the target efficacious dose from the very beginning.

2.2.e Alternative treatment options

The phytotherapy saw palmetto (*Serenoa repens*) is included in the United States Pharmacopoeia (USP) as an acceptable treatment for BPH.[15] The USP concludes that the trials of saw palmetto "provide evidence of moderate scientific quality", but the exact effectiveness of saw palmetto remains in question.

2.2.f Place of product in therapy

Flomax® can be used as first-line therapy for the treatment of the signs and symptoms of BPH.

2.2.g Expected outcomes of therapy

Extensive clinical trials have demonstrated that Flomax® 0.4 mg once daily is effective and well tolerated in the treatment of BPH, significantly increasing urinary flow rate as well as reducing LUTS, even in long-term studies for up to 6 years (see Section 3).

3 SUPPORTING CLINICAL AND ECONOMIC INFORMATION FOR FLOMAX

3.1 Overview of Clinical Trial Program

This section of the dossier provides a review of the clinical evidence for Flomax® in the treatment of benign prostatic hyperplasia (BPH), based on the results from the Flomax® clinical trial program (summarized in Table 2) that involved approximately 4,400 patients. The clinical trials have demonstrated that Flomax is effective in the treatment of BPH based upon statistically significant differences versus placebo in both symptomatology associated with BPH and the objective measurement of urinary flow for up to one year. A number of long-term, open-label, multi-center trials have also demonstrated the safe and effective use of Flomax for maintenance of lower urinary tract symptoms (LUTS) in patients with BPH for up to 6 years. A summary of the short- and long-term clinical trials for Flomax® is provided below.

Table 2. Summary of Flomax Clinical Trial Program

Reference	Study Population	Comparators	Duration	# patients randomized
US Short-Term Trials				
Lepor, 1998a[16]	BPH	Placebo	13 weeks	756
Narayan et al. 1998[17]	BPH	Placebo	13 weeks	735
US Long-Term Trials				
Lepor, 1998b[18]	BPH	Placebo	Extension of 13-week trial an additional 40 weeks	418
Narayan and Lepor, 2001[19]	BPH	None	Extension of earlier trials for additional 64 weeks	949
Study 527.2[20]	BPH	None	Extension of earlier US trials for up to 4 years	609
European Short-Term Trials				
Chapple et al. 1996[21]	BPH	Placebo	12 weeks	575
Abrams et al. 1995[22]	BPH	Placebo	12 weeks	296
European Long-Term Trial				
Schulman et al. 2001[23]	BPH	None	Extension of earlier European trials for up to 4 years	516
Comparator Trials				
Study 527.17[24]	BPH	Terazosin	8 weeks	1,993
Buzelin et al. 1997[25]	Lower urinary tract symptoms suggestive of BPH	Alfuzosin	12 weeks	256
Safety Trials				
Michel et al. 2001[26]	BPH	None	6 months	1,784
de Mey[27]	Normotensive males	Terazosin	15 days	50

3.1.a US Short-Term Trials

Overview

In two multi-center, double-blind, 13-week placebo-controlled Phase III trials conducted in the United States[16,17], Flomax® at daily doses of both 0.4 mg and 0.8 mg was determined to be effective, safe and well-tolerated in the treatment of BPH without the usual cardiovascular effects seen with non-subtype-selective α_1-adrenoreceptor antagonists. A total of 1,491 patients were randomized. The 13-week treatment period was preceded in both studies by a 4-week single-blind placebo run-in period as a way of assessing baselines, compliance and placebo response. During the 13 weeks of treatment, about one-third of the patients received Flomax® 0.8 mg/day (TAM8), one-third received 0.4 mg/day (TAM4) and one-third received placebo. Doses were administered one half-hour after breakfast.

Efficacy

The primary efficacy parameters were: a) change from baseline in total American Urological Association (AUA) symptom scores; b) percentage of patients having an improvement in total AUA symptom score ≥ 25%; c) change in peak urinary flow (Q_{max}) from baseline; and d) percentage of patients with an improvement in Q_{max} ≥ 30%.

In the first study[16], improvement in total AUA symptom score was -9.6 for the TAM8 group, -8.3 for the TAM4 group and -5.5 for the placebo group, respectively ($p < 0.001$ comparing active treatment to placebo). The percentage of patients with an improvement in AUA symptom score ≥ 25% was 74%, 70% and 51% for the TAM8 group, the TAM4 group and placebo group, respectively ($p < 0.001$ comparing active treatment to placebo). The improvement in Q_{max} was 1.78 ml/sec, 1.75 ml/sec and 0.52 ml/sec for the TAM8 group, the TAM4 group and placebo group, respectively ($p < 0.001$ comparing active treatment to placebo). Additionally, the 0.4 mg/day dose demonstrated a rapid onset of action (4 to 8 hours). The percentage of patients with an improvement in Q_{max} ≥ 30% was 36%, 31% and 21% for the TAM8 group ($p < 0.001$ vs. placebo), the TAM4 group ($p = 0.012$ vs. placebo) and placebo group, respectively.

In the second study[17], the mean change in total AUA symptom score improvement was -5.8, -5.1, and -3.6 for the TAM8 group, the TAM4 group and placebo group, respectively ($p < 0.001$ comparing active treatment to placebo). The percentage of AUA symptom score responders was 56%, 55% and 40% for the TAM8 group ($p = 0.001$ vs. placebo), the TAM4 group ($p = 0.002$ vs. placebo) and the placebo group, respectively. The improvement in Q_{max} was 1.79 ml/sec ($p = 0.007$), 1.52 ml/sec ($p = 0.064$) and 0.93 ml/sec for the TAM8 group, the TAM4 group and placebo group, respectively. It is to be noted that the majority of the Q_{max} results involved measurement at approximately trough concentrations of Flomax® (approximately 24 hours following dosing). The percentage of patients with an improvement in Q_{max} ≥ 30% was 33% ($p = 0.027$), 34% ($p = 0.019$) and 24% for the TAM8 group, the TAM4 group and placebo group, respectively.

Safety

In the first study, adverse events with a higher incidence in the Flomax® groups (TAM8, TAM4) relative to the placebo group included: abnormal ejaculation (18%, 6%, and 0%), rhinitis (15%, 12% and 6%), dizziness (11 %, 10% and 5%), and infection (10%, 9% and 5%), respectively. Rhinitis was usually reported as nasal congestion and infection was usually a cold or an upper respiratory infection. The percentage of patients who discontinued treatment due to AEs was 7% for TAM4, 13% for TAM8, and 9% for placebo.

The most frequent adverse events (≥ 10%) observed during the second study were headache, asthenia, pain, infection, back pain, dizziness, abnormal ejaculation, and rhinitis. The incidence of headache was similar and not statistically significant among all three treatment groups. Dizziness, abnormal ejaculation, somnolence and rhinitis were reported more frequently in the TAM8 group. The percentage of patients who discontinued treatment due to AEs was similar across treatment groups.

After the first dose in the first study, orthostatic testing demonstrated that Flomax® did not have a clinically meaningful effect on orthostatic changes in systolic and diastolic blood pressure and pulse rates (standing minus supine). None of the patients in the second study reported adverse events that were similar to the condition called "first dose effect" that has been reported with other α_1-adrenoreceptors antagonists.

A subgroup analysis in both studies did not find a clinically significant effect on vital signs (sitting systolic and diastolic blood pressure and pulse rate) in patients receiving treatment with Flomax® who were hypertensive, or whose hypertension was controlled, or who were normotensive.

3.1.b US Long-Term Trials

Overview

Four hundred and eighteen patients from the first study previously discussed[16] enrolled to continue treatment in a double-blind, 40-week extension study (for a total of 53 weeks of double-blind treatment), which evaluated the long-term use of Flomax® for the treatment of patients with signs and symptoms of BPH.[18] One hundred and forty-four patients were in the TAM8 group, 142 patients in the TAM4 group, and 132 patients received placebo. The same baseline values and primary efficacy parameters used in the first study were also used to assess treatment response in the double-blind extension study.

Because BPH is a chronic condition with treatment typically continuing for years, patients enrolled in the two short-term trials[16,17] and first long-term trial[18] described above were given the opportunity to continue treatment with Flomax (0.4 mg or 0.8 mg/day) in an uncontrolled, open label, multi-center trial designed to evaluate the long-term (> one year) safety and efficacy of Flomax® and monitor changes in therapeutic response over time.[19] A total of 949 patients enrolled in this 64-week extension study (204 patients had completed 53 weeks of scheduled

Flomax® treatment, 352 had completed l3 weeks of scheduled Flomax® treatment, 48 had an unspecified duration of Flomax® treatment, and 345 had no previous exposure as they had been assigned to placebo treatment or they were never randomized to Flomax® treatment in the previous studies. All patients received Flomax® 0.4 mg/day for the first four weeks of the 64-week treatment period. Flomax® dosage adjustments (up to 0.8 mg/day, or up to 0.8 mg/day and then back down to 0.4 mg/day) were permitted after the initial four-week assessment. At some time during the study, 779 patients (82%) received Flomax® 0.8 mg. As in the previous studies, the change from baseline in total AUA symptom scores and Q_{max} were used to assess treatment response.

Finally, data are also available from a four-year, open label, multi-center, extension study[20], which evaluated symptomatic improvement and monitored changes in therapeutic response over time in patients with BPH maintained on Flomax® 0.4 mg/day or 0.8 mg/day. Six hundred and nine patients who had completed the 64-week extension study described above[19] were enrolled in this study. One hundred fifty nine of these patients had received ≥ two years of Flomax® treatment prior to enrollment, making them eligible for ≥ six years of treatment overall. Most patients were treated with both doses of Flomax® during the four-year extension study, and the amount of time a patient was exposed to a given dose varied. Treatment response was assessed in the intent-to-treat population (n = 600) using the same baseline values and primary efficacy parameters from the earlier studies.

Efficacy

The results of the first long-term extension study[18] indicated that the mean change for total AUA symptom score was -9.7, -9.4 and -6.5 for the TAM8 group, the TAM4 group and the placebo group, respectively. The within group changes for each treatment group were statistically significant ($p < 0.001$) compared to baseline. The percentage of symptom score responders was 78%, 81% and 59% for the TAM8 group, the TAM4 group and the placebo group, respectively. The mean change for Q_{max} was 2.1 ml/sec, 1.69 ml/sec, and 0.43 ml/sec for the TAM8 group, the TAM4 group and the placebo group, respectively. These changes for the active treatment groups were statistically significant ($p < 0.001$) compared to baseline. The percentage of Q_{max} responders was 39%, 40% and 22% for the TAM8 group, the TAM4 group and the placebo group, respectively. The efficacy of Flomax® (for both TAM8 and TAM4 groups) observed at the end of the original 13-week study was maintained over the course of the 40 weeks in this long-term study.

In the second long-term extension study[19], the mean change from baseline in the total AUA symptom score and Q_{max} were statistically significant ($p < 0.001$) for all three-month treatment intervals. Improvement in the total AUA symptom score of ≥ 25% was observed in 58% of patients (n = 543) by the third month of treatment and was maintained by 73% of patients (n = 560) after one year of treatment. Improvement in Q_{max} of ≥ 30% was noted in 32- 44% of patients at all three-month treatment intervals. The improvement obtained after three months of treatment for all secondary efficacy parameters (total AUA Bother Score, AUA Irritative Symptom Score, AUA Obstructive Symptom Score, Nocturia AUA Symptom Score Index, total Boyarsky Symptom Score, Boyarsky Irritative Symptom Score, Boyarsky Obstructive Symptom

Score, Nocturia Boyarsky Symptom Score, and Quality of Life Score) was also maintained throughout the course of the study.

During each of the six years of Flomax® treatment in the third long-term study[20], patients demonstrated significant improvement in BPH symptoms compared to baseline. The mean changes in total AUA symptom score and Q_{max} were -8.1 and 2.29 ml/sec, -8.4 and 1.71 ml/sec, -8.2 and 1.93 ml/sec, -8.2 and 1.62 ml/sec, -8.5 and 1.64 ml/sec, and -10.9 and 1.01 ml/sec for years one through six, respectively. The percentage of responders with ≥ 25% improvement in AUA symptom scores was 72%, 74.5%, 72.1%, 71.6%, 73.2% and 80.7%, respectively. The percentage of responders with ≥ 30% improvement in Q_{max} was 40%, 35.8%, 34.4%, 32.8%, 32.9% and 26.9% respectively. Additionally, secondary efficacy parameters were significantly improved from baseline during each of the years of exposure.

Safety

The incidence of treatment-emergent adverse events reported during the course of the 40 additional weeks in the first long-term study[18] was as follows: dizziness was reported in 4% of patients in the TAM8 group, 8% of the TAM4 group and 9% of the placebo group; abnormal ejaculation was reported in 14%, 6% and 0% of patients in each group, respectively. No apparent increase in dizziness or abnormal ejaculation was observed in weeks 14 to 53 compared to the first 13 weeks for Flomax® patients. In addition to abnormal ejaculation, other adverse events with an incidence in either Flomax group of 5% or greater relative to the placebo group were infection, rhinitis and asthenia. The trial data showed that clinically significant orthostatic hypotension was not observed, and that there were no clinically different vital signs changes in both controlled and uncontrolled hypertensive and normotensive patients.

In the second long-term extension study[19], at least one treatment-emergent adverse event was reported by 97% of patients (n = 925) during treatment with Flomax®. The percentage of patients reporting adverse events was greatest during the first three-month treatment interval, with the incidence of adverse events decreasing over the time course of the study. The most commonly reported adverse events were rhinitis (49%), infection (36%), headache (35%), abnormal ejaculation (30%), pain (27%), dizziness (26%), pharyngitis (22%) and increased cough (21 %). Overall 19% of patients (n = 176) discontinued treatment due to side effects. The highest percentage of patients was dropped from the study between the three- and six-month intervals (5%), with the incidence of discontinuation declining relative to the duration of treatment. The most common side effects that led to treatment discontinuation were abnormal laboratory values (3%), dizziness (2%), abnormal ejaculation (2%) and asthenia (1 %). No clinically significant changes from baseline were observed in mean sitting systolic blood pressure, diastolic blood pressure and pulse rate relative to the duration of treatment.

At least one treatment emergent adverse event was reported by 97.2% of patients (n = 587) during the course of the third long-term study.[20] The adverse events most frequently reported were infection (45.5%), accidental injury (29.8%), rhinitis (25.7%), pain (24.8%), pharyngitis (23.8%), headache (18.4%), flu syndrome (17.7%), back pain (16.1%), arthralgia (13.2%), dyspepsia (12.3%), sinusitis (12.1%), prostatic disorder (11.3%), cough increased (10.9%), and

dizziness (10.1%). Other adverse events that occurred less commonly included abnormal ejaculation (8.3%), syncope (1.7%), and postural hypotension (1.3%). Generally, the incidence of adverse events was higher during treatment with Flomax® 0.8 mg (96.9%) than during treatment with Flomax 0.4 mg (78.8%). The overall incidence of adverse events was highest during the ≤ one-year interval; intermediate during the two, three and four year intervals; and lowest in the five and six year intervals. Overall, 15.7% of patients (n = 95) discontinued treatment due to side effects. The most common side effects that led to treatment discontinuation were prostatic disorder (2.8%), PSA increase (1.8%), myocardial infarction (1%), and prostatic carcinoma (1%).

3.1.c European Short-Term Trials

Overview

A meta-analysis of two European double-blind, randomized, parallel group, 12-week trials, compared Flomax® 0.4 mg/day (n = 382), to placebo (n = 193) in patients with BPH.[21] Abrams et al. had previously published the results of one of these studies.[22] Baseline data was established after a 2-week single-blind, placebo run-in period and before randomization to treatment.

Efficacy

A Q_{max} ≥ 30% or ≥ 3 ml/second and a reduction in total Boyarsky symptom score ≥ 25% over baseline were the primary parameters used to determine treatment responders. At endpoint, a Q_{max} response was seen in 32% of the Flomax® group and 20% of the placebo group ($p = 0.003$) based upon ≥ 30% in urine flow. In addition, the baseline Q_{max} in the Flomax® group increased by an average of 1.6 ml/sec (16%) and by an average of 0.6 ml/sec (6%) in the placebo group ($p = 0.002$). The maximum increase in Q_{max} in the Flomax® group occurred at the first assessment (4 weeks), and persisted during the 12 week study period. At endpoint, a total Boyarsky symptom score response was seen in 66% of the Flomax® group and 49% of the placebo group ($p < 0.001$). In addition, the baseline Boyarsky symptom score in the Flomax® group decreased by a total of 3.3 points (35.1%) and by a total of 2.4 points (25.5%) in the placebo group ($p = 0.002$).

Safety

Treatment-emergent adverse effects occurred in 36% of the Flomax® group and 32% of the placebo group ($p = 0.802$). Abnormal ejaculation occurred in more Flomax®-treated patients (4.5%) than in patients receiving placebo (1%) ($p = 0.045$). The vasodilatory adverse events commonly associated with non-subtype-selective α_1-adrenoreceptor antagonists were similar in the Flomax® and placebo groups. There were no clinically relevant effects on blood pressure and pulse rate; however, a mean decrease from baseline of 2.5 mmHg in standing diastolic pressure was observed in the Flomax® group. This was considered to be statistically but not clinically significant. There were no clinically significant changes in blood pressure or pulse rate in

Flomax®-treated patients versus placebo patients. Of note, both hypertensive and normotensive patients with BPH were enrolled in the studies.

In a separate analysis[28] of data from the European short-term trials[21,22], the effect of Flomax® vs. placebo on sexual functioning was evaluated. Sexual function was assessed by related adverse events and by a sexual function score determined from a life-style questionnaire. The results indicated that there was no difference between Flomax® and placebo with regard to the occurrence of decreased libido or impotence (< 2%). Abnormal ejaculation occurred significantly (p = 0.045) more often in the Flomax® group (4.5%) vs. the placebo group (1.0%). However, abnormal ejaculation was not perceived as a major problem by patients since it resulted in few treatment discontinuations (n=3). Compared with the placebo group (+0.49 from baseline of 2.28), there was a significant improvement in total sexual function score in the Flomax group (-0.31 from baseline of 3.35) (p = 0.042).

3.1.d European Long-Term Trial

Overview

Schulman et al. (2001)[23] also reported pooled data from two long-term, open label European studies (an extension of the two short- term studies described above[21,22]) and an extension of a 3-month comparative trial with alfuzosin (discussed in Section 3.1.e)[25] evaluating the efficacy and safety of Flomax® 0.4 mg and 0.8 mg administered once daily after breakfast for LUTS in patients with BPH. Data from 516 patients who remained in the studies for up to four years were analyzed.

Efficacy

The primary efficacy endpoints were the proportion of patients with changes in $Q_{max} \geq 30\%$ or $\geq$ 3 ml/second and a reduction in total Boyarsky symptom score $\geq 25\%$ over baseline. Maximal increases from baseline Q_{max} (achieved by the initial [4- week] assessment during the controlled trials), reductions in total Boyarsky score (achieved by the 14-week assessment during the controlled trials), and the incidence of treatment responders were sustained for up to four years in patients treated with Flomax®. While increases in Flomax® dosage from 0.4 mg to 0.8 mg were permitted after visit three (week 26) if efficacy was not considered optimal and side effects were not reported, no substantial additional benefit was observed in patients receiving Flomax® 0.8 mg (n = 91).

Safety

Treatment-emergent side effects were reported by 76% of patients during the four years of treatment with Flomax®; however only 26% of patients had side effects that were considered possibly or probably related to drug therapy. The most common drug related side effects were abnormal ejaculation (4.3%) and dizziness (5.8%). Other side effects often associated with α_1-adrenoreceptor antagonists occurred at an incidence of < 3%. Overall 17% of patients

discontinued treatment due to side effects, but only 5% of study withdrawals were considered possibly or probably drug related. The most common side effects that led to treatment discontinuation were urinary retention (3.3%), prostatic disorders (1.4%), dizziness (1%) and impotence (1 %). Additionally, small but statistically significant reductions from baseline in supine and standing mean diastolic blood pressure (-2.9 ± 0.5 mm Hg [$p < 0.001$] and -3.8 ± 0.5 mm Hg [$p < 0.001$] respectively) were reported with Flomax® therapy.

3.1.e Comparator Trials

Overview

An open label, multi-center, parallel-design, placebo lead-in study was conducted to evaluate the onset of symptomatic relief and tolerability of Flomax® 0.4 mg/day (n=1,005) compared to terazosin (titrated to 5 mg/day) (n=988) in patients with moderate to severe BPH.[24] All study participants were subject to a three-week placebo lead-in period, followed by 8 weeks of active treatment. Titration of terazosin occurred gradually over two weeks (2 mg/day for one week, then 5 mg/day for the remaining 6 weeks of active treatment).

In a 14-week double-blind, randomized multicenter, parallel group Phase III trial[25], the safety and efficacy of Flomax® was compared with the non-subtype-selective α_1-adrenoceptor antagonist alfuzosin in patients with LUTS suggestive of symptomatic BPH. Following a 2-week placebo lead-in period, patients were randomized to treatment with Flomax® 0.4 mg/day (n=132) or alfuzosin 2.5 mg BID (n=124).

Efficacy

In the study comparing Flomax® with terazosin[24], the results indicated that the mean change in total AUA Symptom Score after four days of active treatment (i.e. the primary efficacy endpoint) was -4.8 (25.3%) for the Flomax group vs. -3.4 (18.1%) for the terazosin group ($p < 0.001$). Only the Flomax® treated patients reached the 25% reduction in BPH symptoms from baseline considered to be clinically significant. Changes from baseline in AUA Symptom Score at Day 19 (four days after terazosin patients began taking the recommended 5 mg dose) demonstrated that Flomax®-treated patients continued to show statistically significant improvements in BPH symptoms versus terazosin-treated patients, both overall (mean change was -8.4 for the Flomax® group vs. -7.5 for the terazosin group, $p = 0.003$) and for those patients with severe BPH symptoms at baseline (mean change was -10.6 for the Flomax® group vs. -9.1 for the terazosin group, $p < 0.001$). Although the trend across all active treatment visits demonstrated continued improvement over time in the signs and symptoms of BPH for both Flomax and terazosin-treated patients, Flomax®-treated patients demonstrated the most pronounced changes in BPH symptoms at earlier visits (Day 5 through Day 19), while terazosin-treated patients only demonstrated comparable changes following titration to the effective dose (5 mg/day) beginning at Day 19.

All post-baseline assessments of total BPH Impact Index, evaluating the patients' perception of the effect of urinary symptoms on quality of life, demonstrated that Flomax®-treated patients

showed a greater improvement relative to terazosin-treated patients. Evaluation of the Investigator's Global Assessment revealed that while both active treatment groups demonstrated improvement relative to baseline, Flomax®-treated patients received a higher proportion of markedly improved or improved ratings at earlier visits (Day 5 through Day 22) than terazosin-treated patients. Differences between Flomax® and terazosin treatment groups were statistically significant Day 5 through Day 15 ($p < 0.001$), Day 19 ($p = 0.012$) and Day 22 ($p = 0.031$). No treatment difference was shown at Day 57 (end of treatment).

In the study comparing Flomax® with alfuzosin[25], both treatments produced comparable, significant ($p < 0.001$) improvements in change from baseline in Q_{max} (1.6 mL/s, 16%) at endpoint. The maximum increase in Q_{max} was obtained within 2 weeks of treatment with Flomax® and between 2 and 6 weeks with alfuzosin. There were also significant ($p < 0.001$) reductions from baseline in total Boyarksy symptom score for both the Flomax® (-4.1, 39.8%) and alfuzosin (03.8, 38.8%) groups (difference between groups not statistically significant).

Safety

In the study comparing Flomax® with terazosin[24], the proportion of patients reporting treatment emergent AEs was similar in both treatment groups (54% and 55.6%, respectively). Terazosin-treated patients reported the following AEs more frequently than did Flomax®-treated patients: asthenia, vertigo, syncope, infection, hypotension, postural hypotension, dizziness, somnolence, impotence, headache and fatigue. Flomax®-treated patients more frequently reported ejaculation disorder and ejaculation failure. Overall, the rate of study discontinuation due to AEs was higher in the terazosin group (6.6%) than in the Flomax group (4.3%).

In the study comparing Flomax® with alfuzosin[25], the frequency of adverse events possibly, probably or definitely related to study medication was 19% for both treatment groups, including the adverse events commonly associated with the hypotensive effects of α1-adrenoceptor antagonists (e.g., dizziness, headache, palpitation/tachycardia). At endpoint there were significant reductions compared with baseline in all mean blood pressure variables in the alfuzosin group but not in patients treated with Flomax®. A subgroup analysis based on age revealed that the larger blood pressure reductions with alfuzosin compared with Flomax were more apparent in elderly patients (ages ≥ 65).

In a separate analysis[28] of data from the Flomax®/alfuzosin comparative study[25], the effect of the two treatments on sexual functioning was evaluated. Sexual function was assessed by related adverse events and by a sexual function score determined from a life-style questionnaire. The results indicated that the incidence of abnormal ejaculation was similar in both treatment groups (< 1%) There was also no difference between Flomax® and alfuzosin with regard to the occurrence of decreased libido or impotence (< 3%). In addition, there was no significant difference in the change in sexual functioning score.

3.1.f Safety Trials

A multi-center, open-label Phase IIIb study[26] with 1,784 patients receiving Flomax® 0.4 mg/day was conducted to detect AEs occurring in 0.15% of patients with 95% confidence. During a total drug exposure time of 811 patient years, 386 AEs were recorded in 253 patients (14.2%; 95% confidence interval [CI] 12.0-15.2%). The AE rate for Flomax® was similar to the AE rates in the placebo arms of the pivotal Flomax® trials. The frequency of AEs in patients without any comedication (n=1,095) was 13.0%. In a logistic regression analysis β-adrenoceptor blockers, converting enzyme inhibitors, antidiabetics and diuretics did not significantly affect the odds ratio for having an AE. However, concomitant α_1-adrenoceptor antagonists (a protocol violation) and treatment with verapamil significantly enhanced the odds ratio for having an AE to 3.87 (CI 1.52 – 9.85) and 3.17 (CI 1.52 – 6.58), respectively.

In a single-center, double-blind, randomized parallel group study[27], the differential impact of Flomax® and terazosin on ambulatory blood pressure (AMPB) and nocturnal orthostatic stress testing (OT) was evaluated. Fifty elderly normotensive male volunteers (mean age 68 years; 27 had LUTS) entered 24-hour placebo run-in followed by a 15-day double-blind treatment period with either Flomax® (0.4 mg once daily at breakfast) or terazosin (once daily in the evening at a dose of 1mg first week, 2 mg the second week, and a final dose of 5 mg). The results indicated that there were significantly fewer Flomax® patients with positive symptomatic OT (n=1) when compared with the terazosin group (n=9, p = 0.011). There were no significant differences between treatments with regard to circadian changes in AMBP or heart rate.

3.1.g Other Studies

Effectiveness and Safety in General Medical Practice

Mann et al. (2000)[29] used prescription-event monitoring data in the UK (1996-1998) to determine drug effectiveness and adverse effects in a non-interventional observational cohort study of over 10,000 patients treated with Flomax® in general medical practice. Patient information, information on adverse events, and an opinion about the effectiveness of the drug were provided by the prescriber (general practitioner) using a standard questionnaire sent 6 months after the initial prescription for Flomax®. The results indicated that Flomax® was considered effective in the treatment of 7,428 (78.3%) of the 9,487 patients in whom the practitioners expressed an opinion about effectiveness. Suspected adverse drug reactions were reported in only 171 (1.4%) of the cohort. Dizziness, headache, malaise and hypotension were the most common adverse reactions.

Effect on Sexual Function

A study by Höfner et al. (1999)[28] evaluated the effect of Flomax® 0.4 mg/day on sexual function in comparison with placebo and alfuzosin 2.5 mg TID, in patients with LUTS suggestive of BPO. Data from 830 patients randomized into three European multicenter studies[21,22,25] were

analyzed. Sexual function was assessed two ways: 1) the number of patients reporting a sexual function-related adverse event and 2) the total score related to sexual function provided by a life-style questionnaire that contained the following questions specific to sexual functioning:

- Has the condition affected your sex life with respect to interest in sex?
- Has the condition affected your sex life with respect to morning erection/quality of erection?
- Has the condition affected your sex life with respect to achieving orgasm/ejaculation?

Any reduction in total score (ranging from 0 to 12 points) at the end of the study implied an improvement in sexual function.

The study results indicated that the only "sexual function"-related adverse event that occurred significantly more frequently in the Flomax® group than in the placebo group was abnormal ejaculation (4.5% vs. 1.0%, $p = 0.045$); however, the abnormal ejaculation was not perceived as a major problem by patients since it resulted in few treatment discontinuations (n=3). There was a significant ($p = 0.042$) improvement in total sexual function score for the Flomax® group (change from baseline [3.35] of -0.31) vs. placebo ([2.28], -.49) at study end. There was no difference between Flomax® and alfuzosin with regard to 1) "sexual function"-related adverse events and 2) change in sexual function score.

Long-Term Risk of Re-Treatment in Naturalistic Setting

de la Rosette et al. (2002)[30] investigated the long-term risk of re-treatment in patients using α_1-receptor antagonists (terazosin, alfuzosin or Flomax®) for the treatment of LUTS. The study reviewed the medical records of 316 newly diagnosed patients who were treated with between February 1992 and June 1998. Treatment consisted of Flomax® 0.4 mg QD (n=96), alfuzosin 2.5 mg TID (n=126), or terazosin 5.0 mg QD. A database was made of initial and follow-up data for up to 5 years. Patients who received any form of re-treatment during follow-up were classified as non-responders, while those who continued using the same type of α-blocker were classified as responders. The results for the whole group indicated that the discontinuation rate was 64% after 3 years and 79% after 5 years of follow-up. The overall re-treatment rate was 38% after 3 and 54% after 5 years of follow-up. The retreatment rates by treatment group were 27% for Flomax®, 37% for alfuzosin, and 49% for terazosin ($p = 0.03$ based on log-rank test). In terms of baseline values, patients receiving Flomax® had a significantly ($p < 0.01$) lower prostate volume (30.5 ± 14.2 ml.) than either alfuzosin (37.5 ± 17.8) or terazosin (40.8 ± 21.6 ml.); and lower prostate volume was shown to correlate with a lower re-treatment rate in the study ($p < 0.001$). A multivariate analysis that controlled for differences in baseline characteristics among the three treatment groups did not find statistically significant differences in the likelihood of re-treatment between Flomax® (odds ratio of 0.59 [95% CI 0.30-1.18] and alfuzosin (reference group), nor between terazosin (odds ratio of 1.16 [0.67-2.01] and alfuzosin. The comparison between Flomax® and terazosin was not reported. It should be noted that the sample sizes in each treatment group were probably too small to detect statistically significant differences.

Impact of Co-Morbidity

Michel et al. (1998)[31] compared the tolerability and blood pressure effects of Flomax® 0.4 mg/day in 19,365 patients with LUTS suggestive of BPO with or without concomitant disease (i.e. hypertension, diabetes, other cardiovascular disease) and/or antihypertensive medication. Patients were identified from two open label, observational, post-marketing studies in Germany. The duration of treatment in Studies 1 and 2 was 4 weeks and 12 weeks, respectively. Global tolerability ratings (very good, good, moderate, poor) were obtained from patients at each visit during the respective treatment periods. The results indicated that in the overall population of Studies 1 and 2, global tolerability at the end of treatment was assessed as very good by 53.1% and 58.8%, good by 40.7% and 38.7%, moderate by 3.6% and 1.6%, and poor by 2.6% and 1.0% of patients, respectively. Patients with concomitant disease reported a slightly poorer tolerability than those without disease ($p < 0.05$) but global tolerability was rated as good or very good in more than 90% and 95% of cases, respectively. Patients concomitantly treated with diuretics, calcium channel blockers or ACE inhibitors reported a slightly lower tolerability than those without co-medication in Study 2 ($p < 0.05$) but global tolerability was rated as good or very good in more than 95% of cases.

3.1.h Review Articles for Treatment of BPH with α_1-Receptor Antagonists

Lowe[32] reviewed 17 placebo-controlled, double-blind trials published in peer-reviewed journals to compare the safety and efficacy of the α_1-receptor antagonists alfuzosin, doxazosin, terazosin, and Flomax®. Trials published only as abstracts or supplements were excluded from the review. The reviewer notes that baseline symptom scores in the different studies varied to a level that could influence the resulting mean changes in symptom scores (i.e. larger reductions occurred with higher baselines, and lower reductions with lower baselines). The results of the review indicated overall that alfuzosin, doxazosin, terazosin and Flomax® provided a comparable range of improvement over placebo in symptom score (5-31%). The range of symptom score reductions was slightly higher for terazosin (9-31%) than for either doxazosin (5-22%), Flomax® (9-20%) or alfuzosin (10-13%). Although the varying definitions of symptomatic response made a direct class comparison problematic, overall a markedly greater proportion of α_1-receptor antagonist patients (approximately 10-30% greater) than placebo patients achieved symptomatic response. While the reviewer considered the overall side-effect profile of the α_1-receptor antagonists to be similar, marked differences were found in the discontinuation rate due to AEs for doxazosin (10-14% versus 2.1-4.2% for placebo) and terazosin (5.9-16% versus 1.6 – 11.4%) versus Flomax® (3-9% versus 3.1-8.0%).

In a similar review, Clifford and Farmer[33] evaluated all randomized, placebo-controlled trials where 1) the treatment intervention for symptomatic BPH included one of the α_1-receptor antagonists, prazosin, alfuzosin, indoramin, terazosin, doxazosin, or Flomax®, or the 5α-reductase inhibitor, finasteride; 2) the treatment duration was at least one month; and 3) at least 30 patients received either active treatment or placebo. The authors concluded that both the α_1-receptor antagonists and finasteride offered significant improvement in both the symptoms of BPH as well as peak urinary flow rates. The authors noted that a meta-analysis of 6 clinical trials showed that treatment with finasteride was only an effective treatment in symptomatic men

with prostate volumes ≥ 40 cm^3. In addition, trials evaluating finasteride and α_1-receptor antagonists for 6-12 months of therapy only demonstrated that the latter offered greater improvements in symptom score reduction (32-49%) than those obtained with finasteride therapy (20-30%), but that the improvement in peak urinary flow rates was similar across both classes of drugs.

De Mey's review[34] of randomized, placebo-controlled trials of the different α_1-receptor antagonists led the author to conclude that although the drugs were similar in efficacy, there were likely differences in terms of tolerability and ancillary cardiovascular effects. Both doxazosin and terazosin reduced blood pressure to a greater extent than did placebo in studies involving hypertensive LUTS patients. For Flomax®, in contrast, the effects on blood pressure in both hypertensives and normotensives with LUTS were consistently not significantly different from placebo; and the author noted that alfuzosin was generally reported to have little effect on blood pressure in LUTS patients compared to placebo.

Michel et al.[35] compared the worldwide experience with Flomax® and alfuzosin. The authors concluded that the efficacy profile of both drugs was very similar. The main difference between the two drugs was the blood-pressure lowering effect of alfuzosin, which the authors noted was mainly noted in studies with the standard and sustained release versions of alfuzosin. Alfuzosin is expected to be marketed in the US based on a new prolonged release (XL) formulation. The authors stated that there is not enough evidence to compare the blood-pressure lowering effects of the XL version of alfuzosin with Flomax®.

3.1.i Summary of HRQL Results from Clinical Trials

In each of the clinical trials involving Flomax®, the impact of treatment on HRQL was evaluated based on a four-item patient lifestyle questionnaire (which later became the BPH Impact Index) that included the following questions: since the last visit

1) how much physical discomfort did any urinary problems cause you?
2) how much did you worry about your health because of any urinary problems?
3) how bothersome has any trouble with urination been?
4) how much of the time has any urinary problems kept you from doing the kinds of things you would usually do?

The scores for each of the four questions were summed to create a total score. A reduction in the total score was translated as an improvement in HRQL. The HRQL results are summarized in Table 3.

Table 3. Summary of HRQL Results from Flomax Clinical Trials

Reference	Comparator	Timeframe	Results for HRQL Total Score
US Trials			
Lepor, 1998a[16]	Placebo	13 weeks	Mean change from baseline significantly greater in each Flomax® group than in the placebo group at study end (-1.8 for placebo, -3.2 for Flomax 0.4 mg/day, -3.6 for Flomax 0.8 mg/day; $p < 0.001$)
Narayan et al. 1998[17]	Placebo	13 weeks	Mean change from baseline significantly greater in the Flomax® 0.8 mg/day group than in the placebo group (-1.40 ± 0.17 vs. -0.56 ± 0.15, $p < 0.001$); results for Flomax 0.4 mg/day group (-0.95 ± 0.15) not statistically significant vs. placebo ($p = 0.089$)
Narayan and Lepor, 2001[19]	Baseline score	53-117 weeks of exposure to Flomax®*	Statistically significant improvements from baseline ($p < 0.001$) were obtained at each 4-week interval throughout the study
Study 527,2[20]	Baseline score	261-325 weeks of exposure to Flomax®*	The change from baseline (mean = 4.5) was consistent across the first five years of exposure (-1.9 to -1.8); the change at the sixth year was -2.3. For every year, the change from baseline was statistically significant ($p < 0.0001$).
European Trials			
Chapple et al. 1996[21]	Placebo	12 weeks	Mean change from baseline larger for the Flomax® group (-3.97 [20%]) vs. placebo (-2.21 [12%]), but not statistically significant (p=NS); individual clusters of worries and concerns ($p = 0.012$) and sexual functioning ($p = 0.042$) were significantly improved in the Flomax group vs. placebo
Schulman et al. 2001[23]	Baseline score	220 weeks	Mean score decreased 6.5 points from baseline of 20.2 (-32%, $p < 0.001$)
Comparator Trials			
Buzelin et al. 1997[25]	Alfuzosin	12 weeks	Both Flomax® and alfuzosin groups had reduction from baseline in HRQL score of 5.2 (27%, $p < 0.001$)

*depending upon which group patients randomized to in placebo-controlled trials

Table 4. Summary of Flomax Clinical Trials

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
US Short-Term Trials			
Lepor, 1998[16]	**Objective** • To evaluate the efficacy and safety of two once-daily doses of tamsulosin (TAM) **Setting** • Multicenter study in US **Design** • Phase III, placebo-controlled, double-blind, randomized, parallel group **Drug Administration** • TAM 0.4 mg/day • TAM 0.8 mg/day (after 1 week of TAM 0.4 mg/day) • Placebo **Study Period** • 13 weeks (excluding 4-week placebo lead-in period)	**Study Sample** **Total:** N = 756 • N = 254 (TAM4) • N = 248 (TAM8) • N = 254 (placebo) **Inclusion criteria** • Men ages ≥ 45 • Total AUA symptom score of ≥ 13 • Bladder outlet obstruction as defined by a peak urinary flow rate (Qmax) between 4 and 15 mL/s • Postvoid residual urine volume < 300 mL **Exclusion Criteria** • History of allergy to α_1-receptor antagonists, alpha-/beta-blockers • "first-dose" hypotensive episode on initiation of alpha-blocker therapy • treatment with finasteride • treatment with any alpha-adrenergic blocking drug, drugs with anticholinergic activity (including antihistamines), or antispasmodic, parasympathetic, or cholinomimetic drugs • concomitant peripheral neurologic, central neurologic, or cardiovascular disease (syncope or pathologic fall within the past year; more than one episode of angina within 6 months; myocardial infarction [MI] within 6 months or ECG evidence of a previous MI ; moderate to severe congestive heart failure; clinically significant cardiac arrhythmias; prosthetic heart valve or cardiac device; or previous history of endocarditis	**Efficacy** Primary efficacy endpoints were (1) change in total AUA symptom score from baseline to endpoint; (2) percentage of patients with improvement in total AUA symptom score ≥ 25%; (3) change in Qmax from baseline; and (4) percentage of patients with improvement in Qmax ≥ 30% • Improvement in total AUA symptom score of -8.3 ± 6.3 (from baseline of 19.8 ± 4.9) for TAM4 and -9.6 ± 6.2 (19.9 ± 4.7) for TAM8 versus -5.5 ± 6.3 (19.6 ± 4.9) for placebo ($p < 0.001$ for both active treatments vs. placebo) • Percentage of patients with improvement in AUA symptom score ≥ 25% was 70% for TAM4, 74% for TAM8, 51% for placebo ($p < 0.001$ for both active treatments vs. placebo) • Improvement in Qmax of 1.8 ± 3.5 for TAM4, 1.8 ± 3.3 for TAM8 versus 0.5 ± 3.3 for placebo ($p < 0.001$ for both active treatments vs. placebo) • Percentage of patients with improvement in Qmax ≥ 30% was 31% for TAM4, 36% for TAM8, 21% for placebo ($p < 0.012$ for TAM4 vs. placebo; $p < 0.001$ for TAM8 vs. placebo) Secondary efficacy endpoints included improvement relative to baseline in (1) primary efficacy measures at the individual double-blind visits; (2) total AUA irritative and obstructive scores; (3) individual AUA symptom scores; (4) total AUA bother score; and (5) total Boyarsky symptom score • Both TAM4 and TAM8 patients had a statistically significantly greater improvement from baseline to endpoint than placebo patients for all

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
			AUA secondary efficacy parameters (except the AUA individual nocturia symptom score for the TAM4 group) • At end point, the mean change from baseline in total Boyarsky symptom score in both the TAM4 and TAM8 groups was significantly greater ($p < 0.001$) than in placebo group **Safety** • The percentage of patients who discontinued treatment due to AEs was 7% for TAM4, 13% for TAM8, and 9% for placebo • AEs with higher incidence in TAM groups relative to placebo group included: abnormal ejaculation (18%, 6%, 0%), rhinitis (15%, 12%, 6%), dizziness (11%, 10%, 5%), and infection (10%, 9%, 5%) in the TAM8, TAM4, and placebo group, respectively
Narayan et al. 1998[17]	**Objective** • To evaluate the efficacy and safety of two once-daily doses of tamsulosin (TAM) **Setting** • Multicenter study in US **Design** • Phase III, placebo-controlled, double-blind, randomized, parallel group **Drug Administration** • TAM 0.4 mg/day • TAM 0.8 mg/day (after 1 week of TAM 0.4 mg/day) • Placebo **Study Period** • 13 weeks (excluding 4-week placebo lead-in period)	**Study Sample** **Total:** N = 735 • N = 248 (TAM4) • N = 244 (TAM8) • N = 239 (placebo) **Inclusion criteria** • Males ages ≥ 45 • Total AUA symptom score of ≥ 13 • Bladder outlet obstruction as defined by a peak urinary flow rate (Qmax) between 4 and 15 mL/s • Postvoid residual urine volume < 300 mL **Exclusion Criteria** • History of allergy to alpha-blockers, alpha-/beta-blockers • "first-dose" hypotensive episode on initiation of alpha-blocker therapy • treatment with finasteride • treatment with any alpha-adrenergic blocking drug, drugs with anticholinergic activity (including	**Efficacy** Primary efficacy endpoints were (1) change in total AUA symptom score from baseline to endpoint; (2) percentage of patients with improvement in total AUA symptom score ≥ 25%; (3) change in maximum flow rate from baseline; and (4) percentage of patients with improvement in maximum flow rate ≥ 30% • Improvement in total AUA symptom score of -5.09 ± 0.41 (from baseline of 17.94 ± 0.37) for TAM4 and -5.76 ± 0.41 (18.22 ± 0.36) for TAM8 versus -3.6 ± 0.37 (19.15 ± 0.39) for placebo ($p < 0.001$ for both active treatments vs. placebo) • Percentage of patients with improvement in AUA symptom score ≥ 25% was 55% for TAM4, 56% for TAM8, 40% for placebo ($p = 0.01$ for both active treatments vs. placebo) • Changes for maximum flow rate represented 15%, 18% and 9% improvement at end point over

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
		antihistamines), or antispasmodic, parasympathetic, or cholinomimetic drugs • concomitant peripheral neurologic, central neurologic, or cardiovascular disease (syncope or pathologic fall within the past year; more than one episode of angina within 6 months; myocardial infarction [MI] within 6 months or ECG evidence of a previous MI ; moderate to severe congestive heart failure; clinically significant cardiac arrhythmias; prosthetic heart valve or cardiac device; or previous history of endocarditis	baseline values for the TAM4 group (1.52 ± 0.23 ml per second), the TAM8 group (1.79 ± 0.22 ml per second), and the placebo group (0.93 ± 0.21 ml per second), respectively (p = 0.007 for TAM8 vs. placebo) • Percentage of patients with improvement in maximum flow rate ≥ 30% was 34% for TAM4, 33% for TAM8, 24% for placebo (p < 0.05 for both active treatments vs. placebo) • TAM patients had a rapid response to treatment – improvement was observed in primary efficacy measures after first week of treatment; change in AUA total symptom score after 1 week significantly greater for TAM4 group vs. placebo (p < 0.05) Secondary efficacy endpoints included AUA irritative and obstructive symptom scores, total AUA bother score, Boyarsky symptom scores and investigator global assessment • Mean change from baseline in AUA irritative symptom score of -1.65 ± 0.18 for TAM4 group, -1.96 ± 0.19 for TAM8 group, 1.18 ± 0.15 for placebo group (p = 0.002 for TAM8 group vs. placebo) • Mean change from baseline in AUA obstructive symptom score of -3.44 ± 0.27 for TAM4 group, -3.80 ± 0.26 for TAM8 group, -2.43 ± 0.26 for placebo group (p < 0.001 for both active treatments vs. placebo) • Mean change from baseline in total AUA bother score of -4.52 ± 0.35 for TAM4 group, -4.88 ± 0.35 for TAM8 group, -2.99 ± 0.37 for placebo group (p = 0.003 for TAM4 group vs. placebo and p < 0.001 for TAM8 vs. placebo) • Mean change from baseline in total Boyarsky symptom score of -2.97 ±

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
			0.26 for TAM4 group, -3.25 ± 0.24 for TAM8 group, -1.89 ± 0.24 for placebo group (p = 0.002 for TAM4 group vs. placebo and p < 0.001 for TAM8 vs. placebo) • Proportion of patients with slight to marked improvement based on investigator global assessment was 60% of TAM4 group, 69% of TAM8 group, and 50% of placebo group (p = 0.005 for TAM4 vs. placebo, and p < 0.001 for TAM8 vs. placebo) **Safety** • The percentage of patients who discontinued treatment due to AEs was similar across treatment groups • Dizziness, somnolence, rhinitis, and abnormal ejaculation were reported more frequently in the TAM8 group (p = 0.05) • There were no significant changes in blood pressure on standing at any visit during study except for a decrease in systolic blood pressure of 20 mm Hg or more between the TAM8 and placebo groups at visit 4 (p = 0.036)
US Long-Term Trials			
Lepor, 1998[18]	**Objective** • To evaluate the long-term efficacy and safety of two once-daily doses of tamsulosin (TAM) **Setting** • Multicenter study in US **Design** • Extension of a 13-week Phase III, placebo-controlled, double-blind, randomized, parallel group trial **Drug Administration** • TAM 0.4 mg/day • TAM 0.8 mg/day • Placebo	**Study Sample** **Total:** N = 418 • N = 142 (TAM4) • N = 144 (TAM8) • N = 132 (placebo) **Inclusion criteria** • Previously fulfilled inclusion/exclusion criteria of the 13-week Phase III trials[16,17] • PSA value 4 μg/L or less at Visit 9 of Phase III study • Acid phosphatase value 2 times the upper limit of normal or less **Exclusion Criteria** • Findings suspicious of prostate	**Efficacy** Primary efficacy endpoints were changes in total AUA symptom score and maximum urinary flow (Qmax) • The improvements in AUA symptom score were greater for the TAM4 group (-9.4) and TAM8 group (-9.7) than the placebo group (-6.5); all groups had statistically significant change from baseline (p<0.001); the difference between groups was not statistically significant • The percentage of responders (decrease in AUA symptom score of 25% of more from baseline) was higher in TAM4 group (81%) and the TAM8 group (78%) than in the

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
	Study Period • 40 weeks	cancer on digital rectal exam	placebo group (59%) • The mean change in Qmax relative to baseline was statistically significant for the TAM4 (1.69) and TAM8 (2.10) groups ($p<0.001$), but not for the placebo group (0.43) Secondary efficacy variables included 1) improvement from baseline in primary efficacy parameters at individual visits; and 2) changes in percentage of responders over time • Comparison of the AUA symptom score values over time showed that the efficacy results at the end of the 13-week Phase III trial were essentially maintained throughout the 40-week double-blind extension phase • In the TAM4 group, the percentage of nonresponders (at week 13) who became responders (at week 53) (43%) was significantly higher than that for responders who became nonresponders (6%); in contrast, for the placebo group, the corresponding percentages were 21% and 23%, respectively **Safety** • The overall incidence of AEs in the TAM4 group similar to placebo group; and the TAM8 group had a higher incidence of AEs than both the TAM4 and placebo groups • The most commonly reported treatment-emergent AE for all groups was infection • There was no systematic relationship between the duration of exposure and the incidence of newly emergent AEs across treatment groups; thus continued exposure to tamsulosin was not accompanied by enhanced risk for adverse events

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

Narayan and Lepor, 2001[19]	**Objective**
	• To evaluate the long-term efficacy and safety of 0.4 mg/day tamsulosin (TAM)
	
	Setting
	• Multicenter study in US
	
	Design
	• Uncontrolled, open-label extension of two 13-week Phase III, placebo-controlled, double-blind, randomized, parallel group trials and one 40-week extension trial
	
	Drug Administration
	• TAM 0.4 mg/day for first 4 weeks
	• TAM 0.4 mg/day, or TAM 0.8 mg/day, or starting TAM 0.8 mg/day and then decreasing back to TAM 0.4 mg/day
	
	Study Period
	• 64 weeks
		Study Sample
		Total: N = 945 ITT
		• N = 608 with TAM exposure
		• N = 347 with no prior TAM exposure
		
		Inclusion criteria
		• Males ages ≥ 45
		• Previously fulfilled inclusion/exclusion criteria of the previous studies
		• Total AUA symptom score of 13 or >=
		• Bladder outlet obstruction (peak urinary flow rate [Qmax] ≥ 4mL/s and ≤ 15mL/s
		• Ability to void a total urine volume of ≥ 125 mL, with a postvoid residual volume ≤ 300 mL
		• Prostrate-specific antigen (PSA) values ≤ 4.0 μg/L, with no clinical evidence of prostrate carcinoma on digital rectal examination (i.e. hard nodules or suspicious areas of the prostrate)
		• PSA values > 4.0 μg/L but ≤ 6.0 μg/L, with no clinical evidence or signs of prostrate carcinoma on digital rectal examination (i.e. hard nodules or suspicious areas of the prostrate) or on trans-rectal ultrasound examination
		
		Exclusion Criteria
		• Drug allergies
		• Use of finasteride, other investigational drugs, or prohibited medications
		• Urinary obstruction due to cancer, calculi, or other disorders
		• Previous transurethral resection of the prostrate
		• Concurrent hypotension
		• Serious concomitant disease
		• Elevated prostrate-specific antigen levels
		  ○ > 6.0 μg/L
		  ○ > 4.0 μg/L and prostrate-specific
			Efficacy
			Primary efficacy endpoints were changes in total AUA symptom score and maximum urinary flow (Qmax)
			• Change from baseline in total AUA symptom score ranged from -5.9 for patients with 0-3 months of TAM treatment to -10.9 for patients with > 24 months of TAM treatment (p<0.001 for both time points)
			• The percentage of responders (decrease in AUA symptom score of 25% of more from baseline) was 58% by month 3 and 84% by month 24
			• Change from baseline in Qmax ranged from 1.42 for patients with 0-3 months of TAM treatment to 2.51 for patients with 18-21 months of TAM treatment (p<0.001 for both time points); the change from baseline was 1.98 at month 24
			
			Secondary efficacy variables included 1) changes from baseline in total AUA bother score and AUA irritative, obstructive, and nocturia symptom scores, 2) total Boyarsky symptom scores and Boyarsky irritative, obstructive, and nocturia symptom scores, 3) average urinary flow rate, and 4) investigators global assessment
			
			• For all secondary efficacy parameters, the improvement obtained after 3 months of treatment was maintained throughout the study (p<0.001)
			• As evaluated by the AUA symptom score, between 43% and 65% of patients reported a decrease in the frequency of nocturia at all intervals
			• As evaluated by the Boyarsky score, between 36% and 60% reported a decrease at all intervals
			• The percentage of patients characterized as improved or markedly improved was between 50% and 66% for all 3-month treatment intervals, as determined by the

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
		acid phosphatase levels more than two times the upper limit of the reference range • Hard nodules or suspicious areas of the prostrate • Evidence or suspicion of a carcinoma on a transrectal ultrasound examination of the prostrate • An episode of acute urinary retention within 4 weeks of study initiation • Urinary tract infection • Instrumentation of the urinary tract (cystocopy or catheterization) • Surgical procedure requiring general anesthesia within 4 weeks of study initiation • Previous evidence of renal dysfunction (elevation in creatinine levels relative to the reference range, confirmed by a repeated test during previous clinical trials) • Previous clinical trial laboratory results • Hemoglobin levels < 12.0 g/dL • Leukocyte counts < 2500/mm^3 • Liver enzyme levels more than three times the established upper limit of normal • Postural symptoms • Blood pressure or pulse rate changes from the last visit of a previous study • Diastolic blood pressure decreases of < 60 mm Hg • Pulse rate > 120 beats/min • Poor compliance in previous studies • Poorly controlled diabetes mellitus	investigator's global assessments **Safety** • Approximately 19% of patients discontinued because of AEs • At least one AE during treatment was reported by 97% of the safety population • AEs reported by > 20% of patients were rhinitis, infection, headache, abnormal ejaculation, pain, dizziness, pharyngitis, and increased cough
Study **527.2**[20]	**Objective** • To evaluate the long-term efficacy and safety of tamsulosin (TAM) > 2 years **Setting** • Multicenter study in US **Design** • Uncontrolled, open-label, Phase IIIB,	**Study Sample** **Total:** N = 609 **Inclusion criteria** • Males ages ≥ 45 • Previously fulfilled inclusion/exclusion criteria of the previous studies • PSA values ≤ 4.0 μg/L	**Efficacy** Primary efficacy endpoints were changes in total AUA symptom score and maximum urinary flow (Qmax) • Change from baseline (17.4) in total AUA symptom score was -8.1, -8.4, -8.2, -8.2, -8.5, and -10.9 for years 1 to 6 respectively; improvement in each year was statistically significant ($p<0.05$),

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

	4-year extension of two 13-week Phase III, placebo-controlled, double-blind, randomized, parallel group trials, a 40-week placebo-controlled extension study and a 1-year open label study
	
	Drug Administration
	• Patients continued on maintenance doses of TAM 0.4 mg/day, or TAM 0.8 mg/day
	• Dosage adjustments (up or down) were allowed during the course of the study at the discretion of the investigator
	
	Study Period
	• Up to 6 years
		Exclusion Criteria
		• Drug allergies
		• Use of finasteride, other investigational drugs, or prohibited medications
		• Urinary obstruction due to cancer, calculi, or other disorders
		• Previous transurethral resection of the prostrate
		• Concurrent hypotension
		• Serious concomitant disease
		• Elevated prostrate-specific antigen levels
		  ○ > 6.0 μg/L
		  ○ > 4.0 μg/L and prostrate-specific acid phosphatase levels more than two times the upper limit of the reference range
		• Hard nodules or suspicious areas of the prostrate
		• Evidence or suspicion of a carcinoma on a transrectal ultrasound examination of the prostrate
		• An episode of acute urinary retention within 4 weeks of study initiation
		• Urinary tract infection
		• Instrumentation of the urinary tract (cystocopy or catheterization)
		• Surgical procedure requiring general anesthesia within 4 weeks of study initiation
		• Previous evidence of renal dysfunction (elevation in creatinine levels relative to the reference range, confirmed by a repeated test during previous clinical trials)
		• Previous clinical trial laboratory results
		• Hemoglobin levels < 12.0 g/dL
		• Leukocyte counts < 2500/mm^3
		• Liver enzyme levels more than three times the established upper limit of normal
		• Postural symptoms
		• Blood pressure or pulse rate changes from the last visit of a previous study
			• The percentage of responders (decrease in AUA symptom score of 25% or more from baseline) ranged from 71.6% to 80.7% during the 6 years.
			• Change from baseline (10.1 ml/sec) in Qmax ranged from 1.01 to 2.29 ml/sec ($p<0.05$ for each year's change).
			• The percentage of responders (a ≥ 30% improvement in Qmax from baseline) ranged from 26.9 to 40.0%, was greatest during the first year, and was maintained across the 6 years of the study.
			
			Secondary efficacy variables included 1) changes from baseline in total AUA bother score and AUA irritative, obstructive, and nocturia symptom scores, 2) total Boyarsky symptom scores and Boyarsky irritative, obstructive, and nocturia symptom scores, 3) average urinary flow rate, and 4) investigators global assessment. Measurement of postvoid residual urine volume and Quality-of-Life (QOL) Index were also included.
			
			• AUA subset scores, Boyarsky scores, and average urine flow rate, showed statistically significant improvement in each year of the study ($p<0.05$).
			• Investigator's Global Assessment demonstrated that 85.2 to 96.3% of patients maintained improvement seen in previous trials or continued to show additional improvement.
			• Improvements in postvoid residual urine volume and in QOL were also maintained through all years of this trial.
			
			Safety
			• 15.7% of patients discontinued treatment due to AEs.
			• At least one AE was reported by 97.2% of patients.

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
		• Diastolic blood pressure decreases of < 60 mm Hg • Pulse rate > 120 beats/min Poor compliance in previous studies	• AEs reported by > 10% of patients were infection, accidental injury, rhinitis, pain, pharyngitis, headache, flu syndrome, back pain, arthralgia, dyspepsia, sinusitis, prostatic disorder, cough increased, and dizziness. • Other AEs that occurred less commonly included abnormal ejaculation (8.3%), syncope (1.7%), and postural hypotension (1.3%). • The incidence of AEs was higher during treatment with TAM 0.8 mg (96.9%) than during treatment with TAM 0.4 mg (78.8%). AEs occurred more frequently during the first 2 years of treatment and diminished as treatment continued.
Europe Short-Term Trials			
Chapple et al. 1996[21]	**Objective** To evaluate the safety and efficacy of tamsulosin 0.4 mg (TAM) vs. placebo in the treatment of symptomatic BHP. **Setting** • Multicenter in Europe **Design** • Meta-analysis of two Phase III randomized, placebo-controlled trials **Drug Administration** • TAM 0.4 mg/day • Placebo q.d. **Study Period** • 12 weeks	**Study Sample** **Total:** N = 575 • N = 382 (TAM) • N = 193 (placebo) **Inclusion Criteria** • Males ages ≥ 45 • LUTS, including hesitancy, poor stream and terminal dribbling, and a diagnosis of BPE • 4 ≤ Qmax ≤ 12 • voided volume of ≥ 120 ml • Boyarsky score of > 6 **Exclusion Criteria** • A consistent residual urine volume of > 400 ml • Previous bladder neck, prostate or pelvic region surgery • Neurological bladder disorder, bladder neck stenosis, urethral stricture, prostate cancer, bladder stone, severe diverticulum of bladder, recurrent urinary tract infection (UTI), or UTI within 1 month of trial commencement • Hepatic or renal insufficiency	**Efficacy** Primary efficacy endpoints were changes in Qmax and total Boyarsky symptom score • Mean increase in Qmax from baseline to endpoint was 1.6 ml/s (16%) in the TAM group vs. 0.6 ml/s (6%) in the placebo group (p=0.002) • At endpoint, 32% of TAM group vs. 20% of placebo group demonstrated a Qmax response ≥ 30% (p=0.003) • The decrease in total Boyarsky symptom score at endpoint was 3.3 points (35.1%) in the TAM group vs. 2.4 points (25.5%) in the placebo group (p=0.002) • Significantly more TAM patients (66%) than placebo patients (49%) had a ≥ 25% decrease in total symptom score at endpoint (p<0.001) Secondary efficacy parameters were Q_{ave}; voiding time; voided volume and residual urine volume; obstructive, irritative, and individual symptom scores; quality-of-life questionnaire and investigator's global

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
		• Significant heart disease within previous 6 months	assessment • Improvement in Q_{ave} in TAM group (0.8) significantly greater than in placebo group (0.4) (p=0.005) • Changes in total (-3.3), obstructive (-2.2), and irritative (-1.1) symptom scores significantly greater for TAM than for placebo (-2.4, -1.7, and -0.7, respectively) ($p \leq 0.017$) • No significant differences were found in voided volume or residual urine volume **Safety** • During a total drug exposure time of 811 years, 386 adverse events (AEs) were recorded in 253 patients (14.2%; 95% confidence intervals). • A total of 149 patients terminated the study prematurely due to AE, and 29 patients suffered from 44 serious AEs, including 5 fatal events (CI 0.12-0.73%). All deaths were judged to be unlikely to be related to study medication
Abrams, 1995[22]	**Objective** To evaluate the efficacy and safety of tamsulosin (TAM) 0.4 mg once daily (as a modified release formula) as compared with placebo in patients with benign prostatic 'obstruction' (symptomatic benign prostatic hyperplasia [BPH]). **Setting** Multicenter study in Europe **Design** Phase III, double-blind, placebo-controlled, randomized, parallel group study. **Drug Administration** • TAM 0.4 mg/day • Placebo **Study Period** • 14 weeks: 12 weeks with a 2 week single-blind placebo run-in period	**Study Sample** **Total:** N = 296 • N = 198 (TAM) • N = 98 (placebo) **Inclusion Criteria** • Males ages ≥ 45 • A diagnosis of benign prostatic enlargement (BPE) and lower urinary tract symptoms (LUTS). • Boyarsky symptom score of >6 • A maximum urinary flow rate (Q_{max}) of ≤12 m/L/s but ≥4 mL/s for a voided volume of ≥120 mL. **Exclusion Criteria** • A residual urine volume of >mL • Previous prostatic bladder neck or pelvic region surgery • A history of neurological bladder disorder	**Efficacy** The primary measures of efficacy were Q_{max} determined from the free-flow measurements, and the total Boyarsky symptom score • The mean increase in Q_{max} from baseline to endpoint was 1.4 mL/s (13.1%) in the TAM group vs. 0.4 mL/s (3.8%) in the placebo group (p=0.028) • The maximum increase in Q_{max} was obtained at the first measurement after 4 weeks of treatment with TAM • The mean decrease in Boyarsky score from baseline was 3.4 (35.8%) in the TAM group vs. 2.2 (23.7%) in the placebo group (p=0.002) Secondary measures of efficacy included the proportion of those with a ≥ 30% improvement from baseline in Qmax, proportion of those with a ≥ 25% decrease in total symptom score, and average

Citation	Study Design	Study Sample and Criteria	Endpoints/Results

	(N=313 before randomization).	• Bladder neck stenosis
		• Urethral stricture
		• Prostatic cancer
		• Bladder stone
		• Severe diverticulum of the bladder
		• Recurrent urinary tract infection (UTI)
		• UTI within 1 month before entry to the study
		• Other conditions which might affect micturition:
		  • Hepatic or renal insufficiency
		  • Significant heart disease
		  • Orthostatic hypotension
		  • Stroke or central nervous system disorders
		  • Hypersensitivity to a α_1-adrenoceptor antagonists.
		  • Exposure to an investigational drug within the previous 3 months or taking concomitant medication that might interfere with the study.
			urinary flow rate.
			
			• Proportion of TAM group with ≥ 30% improvement from baseline in Qmax was 29% vs. 21% of placebo group (p=NS)
			• Significantly more TAM patients (67%) than placebo patients (44%) had a ≥ 25% decrease in total symptom score after 12 weeks (p<0.001)
			• TAM group also had significant improvement in average urinary flow rate (p=0.040)
			
			Safety
			• The incidence of treatment-emergent AEs was similar in TAM and placebo groups (34% and 24% respectively, p=NS)
			• The incidence of cardiovascular-related AEs was similar in TAM and placebo groups (5% and 7%, respectively, p=NS)

Europe Long-Term Trial			
Schulman, 2001[23]	**Objective** • To evaluate the long-term efficacy and safety of once daily doses of tamulosin (TAM) **Setting** • Multicenter study in Europe **Design** • Longitudinal open label extension of 3 randomized, double-blind controlled studies; pooled analysis. **Drug Administration** • TAM 0.4 mg/day • Could be increased to 0.8 mg/day at week 26 and therein after, as needed. **Study Period** • 4 years	**Study Sample** **Total:** N = 516 • N = 421 (TAM 0.4) • N = 91(increased to TAM 0.8) **Inclusion Criteria** • 4 to 12 ml per second maximum urine flow for a voided volume of 120 ml. or greater. • diagnosis of benign prostatic enlargement. • total Boyarsky symptom score greater than 6 points. • a complete set of evaluations available at the clinic visit at the end of the controlled studies. • urinalysis, biochemistry and hematology results within the normal range. **Exclusion Criteria**	**Efficacy** Primary efficacy endpoints were changes in maximum urine flow and total Boyarsky score. • For 0.4 mg/day dose the increase in mean maximum urine flow from baseline was between 1.2 and 2.2 ml. per second (12% and 22%. p<0.001 versus baseline at each time point). Mean maximum urine flow remained predominantly between 11.5 and 12 ml. per second throughout follow-up. For patients who changed to 0.8 mg/day the maximum urine flow at baseline was lower than in those who remained on 0.4 mg (9.4 versus 10.3 ml. per second). The mean maximum urine flow achieved with 0.4 mg. in these patients was less than in those who remained on 0.4 mg. (10.2 versus 12.7 ml. per second). The additional improvement in maximum urine flow at the 0.8 mg. dose was minimal (range

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
		• (all exclusion criteria previously published).	0.2 to 0.7 ml. per second). • The mean total Boyarsky symptom score improved significantly compared with baseline from 6.9 to 9.6 points ($p<0.001$) after 4 weeks, which was the first assessment in the controlled studies. This improvement reached a maximum of 5.4 points after 14 weeks and was sustained for the remainder of tamsulosin treatment ($p<0.001$ versus baseline at each time point). Secondary efficacy endpoints included obstructive voiding, irritative filling, and individual symptom scores, and quality of life questionnaire • Obstructive voiding and irritative filling were significantly decreased from baseline at all visits. • The total symptom score at baseline was 9.3 and 9.6 for the 0.8 mg group and the 0.4 mg groups respectively. For the 0.4 mg/day population the mean decrease in total symptom score from baseline ranged between 4.1 and 4.7 points (43% and 49%) from 14 weeks of treatment and thereafter. For the 0.8 mg/day population the mean total symptom score decreased by 4.2 to 4.8 points (44% to 50%). Increasing the dose to 0.8 mg. had no substantial additional effect on the total symptom score. • The mean total quality of life questionnaire score decreased 6.5 points from a baseline of 20.2 (-32%, $p<0.001$) **Safety** • The only drug related side effects present in at least 3% of patients were dizziness in 5.8% and abnormal ejaculation in 4.3%. • 86 patients (17%) discontinued treatment before 4 years because of side effects. 5% of these study withdrawals were considered possibly

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
			or probably drug related by investigators. The most common side effects in at least 5 patients (1% or greater) that led to the discontinuation of treatment were urinary retention in 17 (3.3%, none considered drug related), dizziness in 5 (1%, all considered drug related) and impotence in 5 (1%, 3 considered drug related). • A total of 117 patients (23%) had serious side effects during TAM treatment for up to 4 years. • Urinary incontinence, angina pectoris, penis disorder, cerebrovascular accident and dizziness developed in only 5 patients (1%) • The most common serious side effects in at least 5 patients were urinary retention in 17 (3.3%), prostatic disorder in 9 (1.7%), angina pectoris in 7 (1.4%), and prostates carcinoma in 7 (1.4%).
Comparator Trials			
Buzelin, 1997[25]	**Objective** To compare the efficacy and tolerability of tamsulosin (TAM) with alfuzosin (ALF) in the treatment of symptomatic BPH **Setting** Multicenter in the Europe **Design** Phase III, double-blind, randomized, parallel group trial. **Drug Administration** • TAM 0.4 mg/day and placebo b.i.d. • ALF 2.5 mg b.i.d. plus a placebo q.d. for two weeks, then ALF 2.5 mg t.i.d. for 10 weeks. **Study Period** 12 weeks with a two week placebo run-in.	**Study Sample** **Total:** N = 245 • N = 126 (TAM) • N = 119 (ALF) **Inclusion Criteria** • Males ages ≥ 45 • Benign prostate enlargement (BPE) • A total Boyarsky urinary symptom score of > 6 and a maximum urinary flow rate (Q_{max}) of ≤ 12 mL/s but ≥ 4mL/s for a voided volume of ≥ 120 mL **Exclusion Criteria** • A consistent residual urine volume of > 400 mL • Previous bladder neck, prostate or pelvic region survey • Any coexisting condition that might affect micturition • Hepatic or renal insufficiency • Significant cardiovascular disease • Cerebrovascular disease or CNS	**Efficacy** The primary efficacy endpoints were maximum urinary flow rate measured by (1) Q_{max} (at least two and a maximum of three free flows) and (2) the total urine symptom score measured by a Boyarsky scale. • There was a significant increase in Q_{max} relative to baseline in both treatment groups at each time of evaluation ($p<0.001$). • At the endpoint, the mean increase in Q_{max} was 1.6 mL/s (166%) for both TAM and ALF groups. The maximum increase in Q_{max} was obtained within 2 weeks of treatment with TAM and between 2 and 6 weeks with ALF. • There were significant reductions from baseline at each time of evaluation in both treatment groups ($p<0.001$) and the mean reduction in total symptom score at endpoint was 4.1 (39.8%) in the TAM groups and 3.8 (38.8%) in the ALF group. Secondary endpoints were the mean

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
		disorders • Life threatening diseases • Previous allergic reactions to α-adrenoceptor antagonsists • Patients were not permitted to take concomitant drugs which could influence the outcome of the study (such as combined α/β-adrenoceptor, α-adrenoceptor antagonists, cholinergic or anticholinergic drugs or calcium antagonists).	urinary flow rate, percentage of patients who had a ≥30% or ≥3 mL/s improvement in Q_{max} from baseline, percentage of patients who were total symptom score responders, irritative, obstructive and individual symptom scores and life-style questionnaire. The effects of TAM and ALF on blood pressure were also measured. • The percentage of patients with a ≥ 30% or ≥ 3 mL/s improvement in Q_{max} and a ≥ 25% decrease in total symptom scores were similar for the two treatment groups at endpoint. A comparable percentage of patients (about 70%) in the two groups were considered to be total symptom score responders. • At the study endpoint both TAM and ALF reduced the total life-style questionnaire score by 5.2 (27%) ($p<0.001$ compared with baseline). • There were no significant differences in obstructive and irritative symptom scores or individual symptom scores between treatment groups. • At endpoint there were significant reductions compared with baseline in all mean blood pressure variables in the ALF group, but not in the TAM group. The differences in the mean changes at endpoint between the treatment groups were about 4.4 mmHg for systolic and 2.7-3.9 mmHg for diastolic blood pressure. A subgroup analysis in elderly (≥65 years) and younger (<years) patients revealed that the larger blood pressure reductions with ALF compared with TAM were more apparent in elderly patients. **Safety** • 14 patients withdrew because of adverse events (AEs). These patients experienced 29 treatment-emergent AEs. In the ALF group, postural

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
			hypotension, dizziness, and vomiting were considered to be definitely, probably or possibly related to medication. In the TAM group, rash, vertigo, postural hypotension and dizziness were considered to be definitely, possibly or probably drug related. • The frequency of AEs possibly, probably or definitely related to study medication according to the investigator was 19% for both treatment groups. The incidence of drop out related to medication for all of the AEs was 2% for ALF and 3% for TAM.
Study 527.17[24]	**Objective** To evaluate the onset of symptomatic relief and tolerability of tamsulosin (TAM) vs. terazosin (TER) in patients with moderate to severe BPH **Setting** • Multi-center in US **Design** • Open label, parallel-design, placebo lead-in study **Drug Administration** All subjects had 3-week placebo lead-in period followed by: • TAM 0.4 mg/day • TER titrated to 5 mg/day **Study Period** • 8 weeks	**Study Sample** **Total:** N = 1,993 • N =1,005 (TAM) • N = 988 (TER) **Inclusion Criteria** • Males ages ≥ 45 diagnose with BPH • Total AUA symptom score ≥ 13 • PSA values ≤ 4.0 μg/L **Exclusion Criteria** • Drug allergies or "first dose hypotensive episode" with alpha-adrenergic blocking agents • Use of finasteride, other investigational drugs, or prohibited medications (including herbal products) • Hypertensive patients using terazosin HCl as monotherapy for both hypertension and BPH • History of peripheral or central neurologic disease, pathological falls, or syncope • History of angina, MI, NYHA Class III/ IV CHF, prosthetic heart valves, cardiac devices, endocarditis, cardiac arrhythmias • Urinary obstruction due to cancer, calculi, or other disorders	**Efficacy** The primary efficacy endpoint was the change from baseline in total AUA symptom score after 4 days of active treatment: • Mean change in total AUA symptom score of -4.8 for TAM vs. -3.4 for TER, representing a 25.3% vs. an 18.1% reduction in BPH symptoms from baseline, respectively at Day 5 ($p < 0.001$) Secondary efficacy endpoints included changes in AUA Symptom Score Index (including subscores), AUA Bother Score Index, BPH Impact Index, and the Investigator's Global Assessment obtained at Day 5, 8, 15, 19, 22, and 57 (end of treatment). • Changes from baseline in AUA Symptom Score Index at Day 19 demonstrated statistically significant improvements in BPH symptoms in the TAM group vs. TER group, both overall ($p = 0.003$) and for patients with severe BPH symptoms at baseline ($p < 0.001$). • TAM-treated patients demonstrated the most pronounced changes in BPH symptoms at earlier visits (Day 5 through Day 19), while TER only demonstrated comparable changes following titration to the effective dose (5

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
		• Previous TURP • Prior pelvic surgery for malignancy or bowel resection • Current diagnosis of prostatitis • History of neurogenic bladder • Serious concomitant disease • Elevated prostate-specific antigen levels > 6.0 μg/L > 4.0 μg/L and prostrate-specific acid phosphatase levels more than two times the upper limit of the reference range • Hard nodules or suspicious areas of the prostate • Evidence or suspicion of a carcinoma on a transrectal ultrasound examination of the prostate • An episode of acute urinary retention within 4 weeks of study initiation • Urinary tract infection • Instrumentation of the urinary tract (cystocopy or catheterization) • Surgical procedure requiring general anesthesia within 4 weeks of study initiation • Previous evidence of renal dysfunction (elevation in creatinine levels relative to the reference range, confirmed by a repeated test during previous clinical trials) • Previous clinical trial laboratory results • Hemoglobin levels < 12.0 g/dL • Leukocyte counts < 2500/mm^3 • Liver enzyme levels more than three times the established upper limit of normal • Postural symptoms • Blood pressure or pulse rate changes from the last visit of a previous study • Diastolic blood pressure decreases of < 60 mm Hg • Pulse rate > 120 beats/min • Poor compliance in previous studies • Poorly controlled diabetes mellitus	mg/day) beginning at Day 19. • AUA Bother Score (evaluating the reduction in perception of BPH symptoms as a problem in patients' lives) revealed statistically significant changes from baseline for Day 5 through Day 22 ($p \leq 0.001$) in TAM vs. TER-treated patients. • Post-baseline assessments of total BPH Impact Index (evaluating patients' perception of the effect of urinary symptoms on quality of life) demonstrated a greater improvement in TAM vs. TER-treated patients. • The Investigator's Global Assessment revealed that while both active treatment groups demonstrated improvement relative to baseline, TAM-treated patients received a higher proportion of markedly improved or improved ratings at earlier visits (Day 5 through Day 22) vs. TER-treated patients. Differences between TAM and TER groups were statistically significant Day 5 through Day 15 ($p < 0.001$), Day 19 ($p = 0.012$) and Day 22 ($p = 0.031$). No treatment difference was shown at Day 57 (end of treatment). **Safety** • The proportion of patients with AEs was similar for TAM (54%) and TER (55.6%) • Treatment emergent AEs reported in both TAM and TER patients with a frequency of >5% included dizziness, headache, rhinitis, and upper respiratory infection • 43 TAM-treated patients [4.3%] and 65 TER-treated patients [6.6%] dropped out of the study due to one or more treatment emergent AEs • AEs leading to study discontinuation were dizziness, rhinitis, and headache; less than 1% of TAM-treated patients discontinued study medication due to abnormal ejaculation

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
Safety Trials			
Michel, 2001[26]	**Objective** To test the safety of tamsulosin (TAM) treatment in a large cohort of men during a prolonged period of time, particularly with regard to comedications. **Setting** • Multicenter in Europe **Design** • Phase IIIb, open-label **Drug Administration** • TAM 0.4 mg/day **Study Period** • 6 months with four office visits	**Study Sample** **Total:** N = 1784 • 543 violated protocol and were excluded from the efficacy analysis (N=1241) • 1241 patients were considered as the key-protocol-point population. Among these, 533 patients had violated the study protocol in minor ways; the remaining 708 patients, who had strictly followed the study protocol, were used as primary population to analyze the efficacy of TAM **Inclusion Criteria** • Diagnosis of LUTS suggestive of BPO by a board-certified urologist • An International Prostate Symptom Score (I-PSS)>7 • The ability and willingness of the patient to follow the protocol and complete the I-PSS questionnaire (German version) sufficiently. **Exclusion Criteria** • A history of bladder neck or prostate surgery • Severe liver insufficiency • Acute urinary tract infection • Other conditions which may affect micturation, orthostatic dysregulation, clinically relevant pathological lab values • Allergic reaction to previously prescribed α_1-adrenoceptor antagonists. • Concomitant use of drugs which could potentially influence the pharmacodynamic properties of TAM with regard to the prostate (other α_1-adrenoceptor antagonist, 5 α-reductase inhibitors, plant extracts intended for the treatment of LUTS suggestive of BPO) was not allowed,	**Efficacy** Primary endpoints were the I-PSS, an interview regarding concomitant medications and a standardized questionnaire on the occurrence of adverse effects (AEs). • The baseline I-PSS was 17.6+/-0.1 for the intent-to-treat population and 17.7+/-0.2 for patients who had strictly adhered to the study protocol. TAM treatment similarly lowered the I-PSS in both populations with the majority of symptom reduction occurring in the first 8 weeks of treatment. • The frequency of AE in patients without any comedication (n=1095) was 13.0% (CI 11.3-14.9%). The most frequent comedications were Ca^{2+} antagonists, β-andrenoceptor blockers, converting enzyme inhibitors, nitrates, antidiabetics and diuretics. In a multiple logistic regression analysis none of these comedications significantly affected the odds ratio for having AEs. However, concomitant α-adrenoceptor antagonist activity significantly enhanced the odds ratio for AE. • The total exposure time was 811 patient years. During this period a total of 386 AEs were recorded in 253 patients (14.2%; CI 12.0-15.2%). The most frequent AEs (occurring in at least 5 patients (0.3%) were dizziness, abnormal ejaculation, headache, hypotension, gastrointestinal disorder, nausea, cardiovascular disorder, impotence, dry mouth, sweating, arrhythmia, postural hypotension, pruritus. A probable, possible or unlikely relationship to study medication was assessed to have occurred in 36%, 39% and 24% of patients respectively. **Safety** • During a total drug exposure time of

Citation	Study Design	Study Sample and Criteria	Endpoints/Results
		if such drugs were used in the past they had to be discontinued for at least three months prior to study entry.	811 years, 386 adverse events (AEs) were recorded in 253 patients (14.2%; 95% confidence intervals). • A total of 149 patients terminated the study prematurely due to AE, and 29 patients suffered from 44 serious AEs, including 5 fatal events (CI 0.12-0.73%). All deaths were judged to be unlikely to be related to study medication.
de Mey et al. 1998[27]	**Objective** To compare the differential effects on ambulatory blood pressure (AMBP) and nocturnal orthostatic stress testing (OT) of tamsulosin (TAM) and terazosin (TER) **Setting** • Single-center in Germany **Design** • Double-blind, randomized parallel-group **Drug Administration** • TAM 0.4 mg/day • TER 1 mg/day 1st week, 2 mg/day 2nd week, final dose of 5 mg **Study Period** • 1-day placebo run-in followed by 15 days of treatment	**Study Sample** **Total:** N = 50 • N = 25 (TAM) • N = 25 (TER) **Inclusion Criteria** • Normotensive males ≥ 60 • With or without LUTS • Considered in general good health based on prestudy screening **Exclusion Criteria** • Any active disease • Prone to orthostatic hypotension	**Safety** 24-hour AMBP, heart rate and OT • No significant differences between groups in regard to circadian AMBP (at study end, change from baseline for systolic blood pressure of -6.29 mm Hg for TAM group vs. -5.42 for TER group (p=NS) • No significant differences between groups in regard to circadian heart rate (at study end, change from baseline for heart rate of 0.10 for TAM group vs. 0.71 for TER group (p=NS) • There were 9 subjects in TER group with symptomatic OT vs. 1 subject in TAM group (p=0.011) • There were 12 subjects in TER group with asymptomatic OT vs. 7 subjects in TAM group (p=NS)

4 MODELING REPORT

4.1 Model Design

The key issue in the design of a cost-effectiveness model for Flomax® compared to other treatment options is to capture the most important elements of alternative treatment pathways as they exist in clinical practice, while retaining conceptual transparency and computational feasibility in the model. Some of the differences in cost-effectiveness across alternative alpha-blocker therapies for BPH will be attributable to differences in drug acquisition costs and differences in the profiles of alternative drug therapies in terms of treatment complexity (dosage frequency, titration) and tolerability (rates of adverse events). These differences in treatment complexity and tolerability across drug therapies may affect adherence to therapy, which in turn will affect both the effectiveness of therapy in clinical practice and its associated costs. The management of adverse events may contribute directly to overall treatment costs, as well as directly affecting health-related quality of life. Thus, the essential elements in a model comparing Flomax® to other drug therapies are those that capture the impact of differences across drugs in the relative simplicity and tolerability of drug therapy over time.

The literature suggests several potential advantages for Flomax® over older, less selective α_1-receptor antagonists in terms of tolerability. Available α_1-receptor antagonists vary in their degree of selectivity for the different α_1-receptor subtypes. Of the α_1-adrenoceptor antagonists (prazosin, terazosin, doxazosin, and Flomax®), only Flomax® is considered to be "prostate specific." Because of its reduced effect on receptor subtypes found in the peripheral vasculature, Flomax® may be associated with fewer adverse effects, such as orthostatic hypotension, asthenia, and syncope.[36]

Several studies have confirmed that Flomax® has negligible effects on blood pressure and does not cause clinically meaningful orthostatic changes.[37,38,39] These negligible effects indicate that the medical services and costs associated with blood pressure monitoring and treatment of blood-pressure–related side effects can be minimized, which is likely to improve Flomax® cost-effectiveness relative to other α_1-receptor antagonists.

A retrospective cohort study[40] assessed the occurrence of hypotensive-related events, including falls and fractures, associated with use of terazosin, doxazosin, and prazosin. Using prescription drug and medical utilization information from pension plan health claims data, Chrischilles and colleagues evaluated the incidence of adverse effects with the use of nonselective α_1-receptor antagonists in men with and without hypertension. Patients were 65 years of age and older and had a diagnosis of BPH at some time during the 3-year study period (January 1995 through December 1997). Rates of possible hypotensive events were compared before and after drug initiation in men who began therapy with an α-antagonist during the study period. Potential hypotensive events included syncope, postural hypotension, vertigo, fractures, and other injuries. The effects of age, presence or absence of hypertension, and risk factors for hypertensive effects were controlled for in the analysis. Data for 1,277 men were evaluated (211 with a diagnosis of hypertension and 1,066 without this diagnosis).

The study found a significant increase in hypotensive events after α-antagonist initiation. Overall, the incidence of hypotensive events increased from 2.4 per 10,000 patient-days to 3.2 per 10,000 patient-days. This increase occurred in both the hypertensive and the normotensive patient subgroups (2.8 to 4.2 events and 2.4 to 3.0 events per 10,000 patient-days, respectively). There was also a significant increase in injuries observed after α-antagonist initiation. The investigators concluded that initiation of nonselective α-antagonists increases the risk of hypotension-related clinical events that are consistent with vascular α-adrenoreceptor blockade.

Basic Model Structure:

The basic flow of treatment options in the decision model used to evaluate the cost effectiveness of Flomax is illustrated in Figure 1. Treatment is initiated with Flomax®, terazosin, or doxazosin. Patients at initiation are defined as new to pharmacological therapy and have AUA symptom scores in the moderate range at baseline.

After the first 6 months of initial therapy, treatment is either successful or unsuccessful. Treatment success is defined as obtaining and maintaining a 25% improvement in AUA symptom score from baseline. A therapy may "fail" for a variety of reasons. In some cases the desired result is not obtained despite appropriate use, but in many cases failure is related to discontinuation of use – either due to adverse events or other reasons. The likelihood of failure in usual clinical practice is likely to differ from that observed in clinical trials. For example, more patients will discontinue therapy in clinical practice than in clinical trials for reasons other than adverse events. Thus, efficacy estimates from 'intent to treat' analyses of clinical trial data are likely to overstate the rate of treatment success in clinical practice. For this reason, any differential discontinuation across alternative therapies can have a profound impact on their effectiveness.

In the 2-year base-case model, if the initial therapy is successful at 6 months, the patient continues on the therapy and is re-assessed in increments of 6 months. The model can also be run with a minimum time period of 1 year and a maximum of 3 years. In the decision model, if the initial drug therapy has to be discontinued due to an adverse event the patient is switched to finasteride (monotherapy); except in the case of a hypotensive adverse event while initiating therapy with terazosin or doxazosin. In this case, the patient would be switched to Flomax® (monotherapy) and follow the Flomax® treatment algorithm from this point forward. If the initial therapy "fails" for any reason other than an adverse event, finasteride is added to the initial therapy (combination therapy). If the new therapy is successful at the end of a 12 month period, the patient remains on the new therapy. The 6 month treatment assessment interval follows Cockrum et al.[41] and is based on the slower onset of effect for finasteride compared to α_1-receptor antagonists.

If the new (mono or combo) therapy fails, the patient then progresses to transurethral resection of the prostate (TURP). If TURP is not successful (in terms of AUA symptom score improvement), the patient has a repeat TURP. However, patients undergoing TURP also are at risk for permanent adverse effects of TURP, such as incontinence or impotence.

The primary effectiveness measure employed in the decision model is therapy success at 2 years on initial therapy (i.e., no finasteride switch/add). Patients initiating therapy will be at risk for any adverse events associated with therapy. The specific types of adverse events and levels of risk are related to the specific therapy evaluated. Adverse events, when they occur, have two implications in the model. First, some adverse events, such as hypotension, may directly generate excess resource utilization and costs, thereby increasing overall treatment costs. Second, adverse events may require a modification of therapy, with increased medical management costs.

The occurrence of minor adverse events also may affect patient decisions to persist on therapy, which may affect both the cost and effectiveness of therapy. Similarly, more complex therapies (those requiring more titration, more frequent dosing, etc.) are likely to yield lower adherence than less complex therapies, which in turn may reduce effectiveness.

All of these model events have some impact on the costs of treatment for patients initiating a specific therapy. The model accumulates these costs for patients along each potential treatment path, thus allowing for comparison of total treatment costs across the three initial therapies. Incremental cost-effectiveness ratios may be derived from the total cost and effectiveness measures.

Model Parameters:

Specific values for model parameters used for the base-case analysis are reported in Table 5.

The first set of model parameters relate to the clinical efficacy of each of the three initial therapies. Based on Agency for Healthcare Research and Quality (AHRQ), formally know as the Agency for Health Care Policy and Research (AHCPR), meta-analysis by McConnell et al[42], the initial treatment efficacy was assumed to be 74% for terazosin and doxazosin. Following Lepor et al.[38] initial treatment efficacy was assumed to be 81% for Flomax®.

To translate these initial efficacy estimates into initial effectiveness estimates, an additional discontinuation factor (above that observed in clinical trials) is used. It is possible that the tolerability advantages of Flomax® over the non-prostate-specific α_1-receptor antagonists translate into greater adherence to therapy in usual clinical practice. However, there are no published studies with analyses of data from usual clinical practice to confirm this possibility. Therefore the base-case model assumes an additional 10% discontinuation rate in the initial period for all three treatment options to account for potential decreases in 'real world'.

Another factor that may affect both effectiveness and cost is the percent of patients on each drug with twice per day (BID) compared to once per day (QD) dosing. Although BID dosing is not recommended for any of these drugs for the treatment of BPH, Raymond and Smith[43] find BID use rates of 17% for terazosin and 38% for doxazosin in clinical practice. It is likely that BID dosing is used to minimize the risk of hypotensive events. To be conservative, the base-case model assumes 10% BID use among BPH patients for both terazosin and doxazosin. The base-case model assumes no BID dosing for Flomax since these orthostatic changes have not been

observed with Flomax®.[37,38,39] A study by Paes and colleagues[44] reveals that BID dosing is associated with lower rates of adherence to therapy than QD dosing. This effect is captured in the model by assuming that the risk of discontinuation for BID dosing is 1.33 times the risk for QD dosing. The extent of BID dosing has an even more direct impact on costs, as drug acquisition costs per pill for all of these drugs are approximately the same for all dosage strengths. Therefore BID dosing is associated with about twice the drug acquisition costs of QD dosing.

Drug-induced hypotension also can have direct cost effects. Chrischilles and colleagues[40] found excess rates of resource utilization among new users of nonselective α_1-receptor antagonists consistent with hypotensive episodes – often sprains and fractures associated with falls. The distribution of diagnosis codes in these cases was used to estimate the cost per excess fracture and non-fracture episode.

The need for titration can also affect costs due to the more intensive effort required to manage medical therapy. In the model, patients who initiate therapy with terazosin are assumed to begin with 2 mg for 10 days, then 5 mg for 10 days, and then 10 mg per day thereafter. The base-case model assumes 10% of this final stage is 5 mg BID. Patients who initiate therapy with doxazosin are assumed to begin with 4 mg for 10 days and then 8 mg per day thereafter. The base-case model assumes 10% of this final stage is 4 mg BID. These titration schedules are more rapid and entail fewer steps than in most previously published models (e.g., Cockrum et al.[41]), as these less conservative titration schedules are more likely to be consistent with usual practice. In contrast, patients initiating therapy with Flomax® are assumed to take 0.4 mg QD with no titration or BID dosing in the base-case model.

Drug acquisition cost estimates are based on average wholesale prices (AWP) for each of the dosage strengths for each of the drugs. AWP prices were obtained from the "Red Book." For the brand name drugs, there is only one AWP for each of the dosage strengths. However, both of the generic drugs have several different manufacturers with differing AWPs. For doxazosin, this is a minor issue since most of the generic AWPs are similar, but for terazosin there was considerable variation in AWPs across manufacturers. To be conservative, AWP estimates for the generic drugs are based on the three lowest-price manufacturers in terms of AWP. The resulting estimate may be lower than a market-share weighted average AWP, particularly for terazosin. In all cases, drug prices in the base-case model are calculated by average AWP less 15 percent.

In the base case scenario, a pure payer perspective is represented which subtracts patient co-payments from the direct medical cost calculation. The specific co-pay levels usually differ for generic vs. brand name drugs, with a higher co-pay amount for brand name drugs (i.e., a "two-tier" co-payment design). Many managed care plans have three patient co-pay tiers: generic, preferred brand name drugs, and non-preferred brand name drugs. In the model, both terazosin and doxazosin are available as generic drugs, but Flomax® and finasteride are not. Thus, from the perspective of a managed care payer, differential patient co-pays would apply to the generic vs. brand name drugs. In the base-case scenario, the generic co-pays are $7 and the brand co-pays are $15. These co-pays can easily be adapted to represent a specific health plan.

Additionally, the co-pay option can be eliminated. If removed, total direct costs would be representative of plan costs combined with patient costs.

Estimates of unit costs for various resources used in the treatment of BPH were obtained from the literature, primarily as summarized by Cockrum et al.[41] and Ackerman et al.,[45] and estimates of rates of complications for TURP were obtained from several sources,[46,47,48,49,50] as noted in Table 5. The estimated cost for TURP used in the base-case is an incidence-rate weighted average of costs associated with various surgical complications of TURP.

All costs are discounted using an annual discount rate of 3.0%, or 1.5% each six-month cycle following the first year of treatment.

4.2 Model Results

The model results for the base-case scenario are presented in Table 6. The costs represent direct costs from a payer perspective by subtracting the patient co-payments from the total cost of BPH treatment over two years after initiating therapy. The estimated payer total direct costs when using a generic co-pay of $7 per month and a brand co-pay of $15 per month are: $2,854 for Flomax, $2,934 for generic terazosin, and $2,958 for generic doxazosin. Measuring initial medical treatment success at 2 years as the effectiveness measure, the base-case model predicts that medical success is achieved for 65.30% of patients initiating therapy with Flomax®, compared to 57.59% for terazosin or doxazosin. Since Flomax is less expensive and has a higher effectiveness rate after two years compared to terazosin and doxazosin, they are both dominated by Flomax® and have a negative incremental cost-effectiveness ratio (ICER).

An easy adaptation to the model is to keep all variables in the base-case scenario the same, except the removal of patient co-pays from the equation. This scenario represents a patient co-pay of zero, providing a cost perspective of the payer without any contribution from the patient. Model results are shown in Table 7. The total direct medical costs over two years on initial therapy are $3,210 for Flomax®, $3,157 for doxazosin, and $3,134 for terazosin. Medical treatment success after two years remains the same since the only change was the exclusion of co-pays. Therefore, similar to the previous example, effectiveness is the same for terazosin and doxazosin but since terazosin costs less, doxazosin in dominated by terazosin. Comparing Flomax® to terazosin, the cost and effectiveness comparison per patient in terms of ICER is $992.

Another way to assess this scenario from a payer's perspective is by comparing only the differences in costs, keeping in mind that Flomax has a higher success rate. The 2 year incremental cost for Flomax® versus terazosin is $76, which equals $38 annually. Therefore a monthly co-pay difference of $4 for Flomax® versus terazosin would off-set the cost for the payer. The monthly co-pay difference needed as a cost off-set for Flomax® versus doxazosin would be even less since the 2 year incremental cost difference is only $53.

Additional one-way sensitivity analyses were run with the model to test the amount of uncertainty in the base case scenario. The following variables were altered as specified: the

model time frame was extended to 3 years, published clinical trial data was used versus adjusting for 'real world' effectiveness, BID dosing was assumed to be zero for the generics, titration visits were assumed to be 2 for each generic versus 3 for terazosin, and the chance of the either doxazosin or terazosin having a hypotensive event was assumed to be zero. In all of these cases, doxazosin and terazosin were dominated by Flomax®, which had better success rates and lower costs.

The following scenarios were sensitive to changes in the base-case model results when variables were modified. As mentioned previously, removal of the patient co-pay from the equation results in an ICER of $992 for Flomax® versus terazosin and is shown in Table 7. Additionally, decreasing the co-pay to $5 for generic and $10 for brand, results in an ICER of $229 for Flomax® over terazosin. A third scenario tested a zero percent chance of having a fracture with a hypotensive adverse event and the ICER for Flomax® over terazosin was $430.

4.3 Discussion

No "league tables" for incremental costs per successful medical treatment of BPH are available. Cockrum et al.[7] find costs per treatment success (compared to watchful waiting) of about $1,500 to $2,000 prazosin, compared to $1,800 to $2,800 for terazosin or doxazosin, and about $2,100 to $3,500 for finasteride (expressed in 2001$). Because all three α_1-receptor antagonists in their model are treated as equally effective, the differences in cost estimates across α_1-receptor antagonists are entirely attributable to differences in drug acquisition costs. No incremental cost-effectiveness ratios are reported in the Cockrum et al. paper, but using the reported cost and effectiveness estimates, the incremental cost per treatment success would be over $3 million for finasteride vs. prazosin (the lowest-cost alpha blocker). Note that "treatment success" as defined in the Cockrum et al.[41] model includes success achieved via TURP after medical therapy failure.

Moving to the results for "cost per medical treatment success," despite the lack of a well-accepted benchmark, it may be reasonable to speculate that an incremental cost of $2000 or $4000 may represent a reasonable amount to pay to avoid surgery for 2 years, given the risks of permanent undesirable consequences associated with surgery. A model with an extended time horizon and utility ratings for health states could be used to develop an estimate of incremental "cost per QALY" to compare to usual benchmarks. However, the 2 year time horizon is too short to yield estimates appropriate for such comparisons.

Although doxazosin is consistently dominated in the results above, sensitivity analyses indicate that the estimated 2 year costs for terazosin relative to doxazosin are very sensitive to drug acquisition costs. Thus, any preference for generic terazosin vs. generic doxazosin on a cost-effectiveness basis would be simply based on lower drug acquisition costs under most circumstances.

The issue of appropriate "willingness to pay" benchmarks is moot in the base case-scenario if the analysis takes a pure payer perspective where the payer's drug benefit design is presumed to incorporate a typical $7 (or greater) generic vs. branded drug co-pay differential. Under these

conditions, as reported in Table 6, from the payer's perspective Flomax® is less costly and more effective than either generic terazosin or generic doxazosin. In other words, terazosin and doxazosin are dominated by Flomax® as a treatment option.

An important limitation of the model is the measurement of treatment effectiveness. Although a simple measure such as "successful medical therapy" has an intuitive appeal, some potentially relevant health benefits are missed by this measure that may accrue differentially across therapies. For example, the model captures the cost impact of hypotensive episodes resulting in resource utilization, but there is no direct effect of such cases on the measure of treatment "effectiveness." However, it seems reasonable to suggest that, even if equally effective in treating BPH in terms of AUA symptom score, a therapy that may result in a fracture from hypotensive-related falls should be regarded as "less effective" overall than one that does not. A more refined measure of effectiveness would further enhance the cost-effectiveness.

4.3 Summary

A decision model was designed to evaluate the costs and effectiveness of Flomax®, terazosin or doxazosin as initial therapies for BPH as used in clinical practice. In the base-case model scenario, Flomax® is more effective than terazosin or doxazosin, where effectiveness is defined as the percentage of patients initiating therapy for which medical therapy remains successful for 2 years. As the base-case analysis is viewed from a pure payer perspective, Flomax® has lower payer costs over 2 years than either terazosin or doxazosin where generic and brand drug co-pays are $7 and $15, respectfully. If the model runs a broader perspective above the pure payer costs, patient co-pays are not taken into account. Total direct medical costs, over 2 years for Flomax® are projected to be approximately $53 and $76 greater than projected costs for doxazosin or terazosin, respectively. This results in an ICER of $693 and $992 per additional patient success for doxazosin and terazosin, respectively. In addition, this incremental cost could be off-set by a monthly co-pay difference of $4 for Flomax® versus doxazosin or terazosin.

Figure 1: Model Flow Diagram

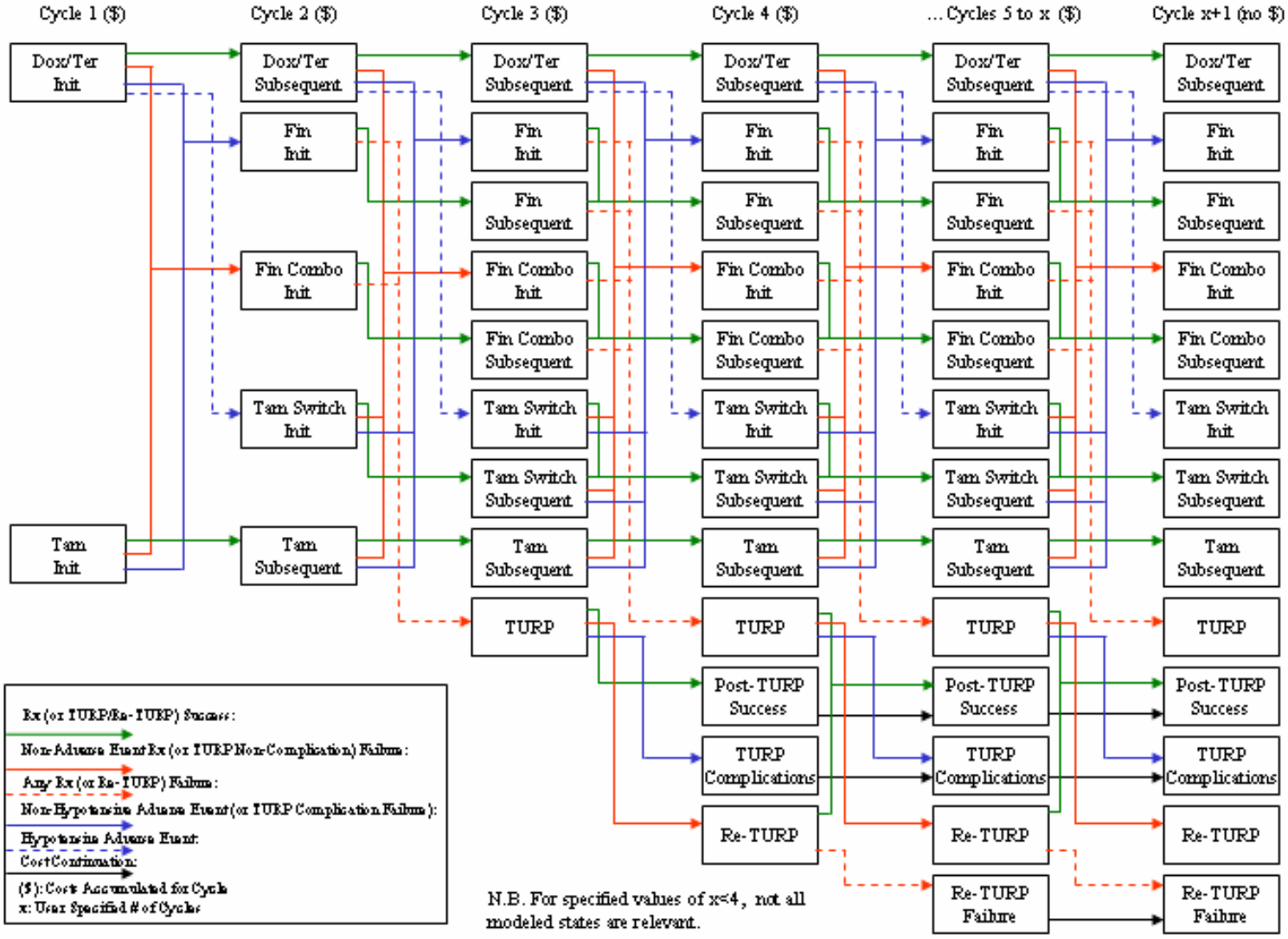

Table 5. Summary of Parameter Values Used in Model

Therapy	Effectiveness (Success Rate)	Source (Rate)	Cost	Source (Cost)	Notes
Doxazosin	63.7 %	McConnell 1994	$0.82/pill	Average 2002 AWP of 3 lowest prices	Converted from published efficacy to effectiveness by subtracting 10% discontinuation not due to adverse events; 10% BID assumed, 1.33 BID discontinuation multiplier used.
Terazosin	63.7 %	McConnell 1994	$0.75/pill	Average 2002 AWP of 3 lowest prices	
Flomax®	71.0 %	Lepor 1998	$1.62/pill	2002 AWP	
Subsequent doxazosin	96.5 %	Cockrum 1997; Raymond 1997	$0.82/pill	Average 2002 AWP of 3 lowest prices	
Subsequent terazosin	96.5 %	Cockrum 1997; Raymond 1997	$0.75/pill	Average 2002 AWP of 3 lowest prices	
Subsequent Flomax®	97.2 %	Djavan & Marberger 1999	$1.62/pill	2002 AWP	
Switch to Flomax®	60.0 %	Assumption	$1.62/pill	2002 AWP	
Finasteride - Switch	25.0 %	Baladi, 1996; Stoevelaar, 2001	$2.26/pill	2002 AWP	Rate is based on difference between finasteride and placebo in clinical trials.
Finasteride - Add-on	30.0 %	Expert Opinion	$2.26/pill	2002 AWP	
Subsequent finasteride or combo	95.0 %	Cockrum 1997			
TURP	88.0 %	Cockrum 1997	$6,066.10	Ackerman 2000	TURP success rates are provided on the condition that no serious permanent complications occurred Costs adjusted to 2002$ from 1999$ using 1.1397; Weighted average cost for potential TURP outcomes;
Re-TURP	50.0 %	Cockrum 1997	$6,066.10	Ackerman 2000	
TURP Complications	**Rate**	**Source (Rates)**	**Cost**	**Source (Cost)**	**Notes**
Erectile Dysfunction	6.00 %	Ackerman 2000	$2,701.09	Ackerman 2000	TURP costs shown are based on published costs five year study costs. One-tenth of the weighted average of these complication costs is included in every 6 month cycle following a complication occurrence. Costs adjusted to 2002$ from 1999$ using 1.1397; The primary sources for TURP complication rates can be found in Ackerman.
Incontinence	2.00 %	Ackerman 2000	$1,340.29	Ackerman 2000	
Bladder Decompensation every per 4 weeks	0.50 %	Ackerman 2000	$5,141.19	Ackerman 2000	
Bladder Decompensation every 7 weeks	0.50 %	Ackerman 2000	$3,259.54	Ackerman 2000	
Other Serious Complications	1.00 %	Ackerman 2000	$567.57	Ackerman 2000	
TURP Death Rate	0.10 %	Ackerman 2000			

Physician & Lab	**Frequency**	**Source (Frequency)**	**Cost**	**Source (Cost)**	**Comments**
Regular GP check-up visit	Every 6 months	Cockrum 1997	$42.30	Cockrum 1997	Adjusted to 2002$ from 1994 $31.25; 1 additional visit for non-hypotensive AEs
GP Titration Visit ▪ Flomax® ▪ doxazosin ▪ terazosin ▪ finasteride	 1 2 3 1	Expert Opinion	 $ 30.04 $ 60.08 $ 90.12 $ 30.04	Cockrum 1997	
Urologist visit	Pre-TURP	Cockrum 1997	$ 83.75	Cockrum 1997	Adjusted to 2002$ from 1994 $61.87
Urologist visit	Post-TURP	Cockrum 1997	$ 52.87	Cockrum 1997	Adjusted to 2002$ from 1994 $39.06
Serum creatinine	Baseline & 12 m	Cockrum 1997	$ 21.66	Cockrum 1997	Adjusted to 2002$ from 1994 $16.00
Urinalysis	Baseline & 12m	Cockrum 1997	$ 29.78	Cockrum 1997	Adjusted to 2002$ from 1994 $22.00
PSA level	Baseline	Cockrum 1997	$ 66.33	Cockrum 1997	Adjusted to 2002$ from 1994 $49.00
Uroflowmetry	Pre-TURP	Cockrum 1997	$ 74.45	Cockrum 1997	Adjusted to 2002$ from 1994 $55.00
Post-void residual	Post-TURP	Cockrum 1997	$ 128.59	Cockrum 1997	Adjusted to 2002$ from 1994 $95.00
Hypotensive AE	**Rate**	**Source (Rate)**	**Cost**	**Source (Cost)**	**Comments**
Doxazosin Initial 6 month	4.00 %	Chrischilles 2001			0.9 x 4.4% found in Chrischilles 2001
Doxazosin subsequent	0.25 %	Expert Opinion			
Terazosin Initial 6 month	4.80 %	Chrischilles 2001			1.1 x 4.4% found in Chrischilles 2001
Terazosin subsequent	0.30 %	Expert Opinion			1.2 times doxazosin
Hypotensive AE w/fracture	25.00 %	Chrischilles 2001	$8,960.00	Chrischilles 2001	Estimated from distribution of fracture diagnoses per Chrischilles
Hypotensive AE w/out fracture	75.00 %	Chrischilles 2001	$ 261.73	Chrischilles 2001	Estimated from distribution of fracture diagnoses per Chrischilles
Non-Hypotensive AE	**Rate**	**Source (Rate)**	**Cost**	**Source (Cost)**	**Comments**
Initial 6-month rate for all alpha-blockers	1.5 %	Djavan & Marberger 1999			Published for terazosin, assumed the same for doxazosin and Flomax®
Post 6 month subsequent rate for all alpha-blockers	0.5 %	Assumption			Published for terazosin, assumed the same for doxazosin and Flomax®

Table 6. Projected Two-Year Costs, Effectiveness, and Incremental Cost-Effectiveness, Payer Costs (Direct Cost Less Patient Rx Co-Pays -- $7 generic, $15 brand)

Initial Therapy	Cost	Success Rate	ICER (Flomax vs. generic)
Flomax®	$ 2,854	65.30 %	
terazosin	$ 2,934	57.59 %	Dominated
doxazosin	$ 2,958	57.59 %	Dominated

Table 7. Projected Two-Year Costs, Effectiveness, and Incremental Cost-Effectiveness, Total Direct Medical Costs (Payer Costs with Zero Patient Costs)

Initial Therapy	Cost	Success Rate	ICER (Flomax vs generic)
terazosin	$ 3,134	57.59 %	$992
doxazosin	$ 3,157	57.59 %	$693
Flomax®	$ 3,210	65.30 %	

5 VALUE SUMMARY FOR FLOMAX

The preceding sections of this dossier have presented the clinical and pharmacoeconomic evidence supporting the acceptance and use of Flomax® in the treatment of the signs and symptoms of BPH. This section provides a summary of the clinical evidence for Flomax® and presents the rationale for why Flomax® provides the best value to health plans of any α_1-adrenoceptor antagonist used in the treatment of the signs and symptoms of BPH.

5.1 Clinical Evidence for Flomax

The key findings from the Flomax® clinical trial and Phase IV programs were as follows (see Section 3):

- Flomax® was significantly better than placebo in treating the signs and symptoms of BPH
  - Improvement in total AUA symptom score of -8.3 for Flomax® vs. -5.5 for placebo in one pivotal trial ($p < 0.001$), and -5.1 for Flomax® vs. -3.6 for placebo in a second pivotal trial ($p < 0.001$)
  - Percentage of AUA symptom score responders (i.e. $\geq$ 25% improvement from baseline) was 70% for Flomax® vs. 51% for placebo in one pivotal trial ($p < 0.001$), and 55% for Flomax® vs. 40% for placebo in a second pivotal trial ($p = 0.002$)

- The efficacy improvements found with Flomax® were maintained for up to 6 years
  - Mean change from baseline in total AUA symptom score was -8.1, -8.4, -8.2, -8.2, -8.5, and -10.9 for years one through six, respectively ($p < 0.05$)
  - Percentage of AUA symptom score responders was 72%, 74.5%, 72.1%, 71.6%, 73.2% and 80.7%, respectively.

- In a head-to-head randomized trial, Flomax® demonstrated superiority to terazosin in treating the signs and symptoms of BPH
  - Mean change in total AUA symptom score after four days of active treatment (i.e. primary efficacy endpoint) was -4.8 (25.3% improvement) for Flomax® vs. -3.4 (18.1%) for terazosin ($p < 0.001$)
  - Change from baseline in AUA symptom score at Day 19 (four days after terazosin patients titrated to effective dose of 5 mg/day) continued to be significantly ($p = 0.003$) higher for Flomax® (-8.4) vs. terazosin (-7.5)
  - Flomax® and terazosin provided comparable improvements in AUA symptom scores for the remainder of the study
  - All post-baseline assessments of total BPH Impact Index, evaluating the patients' perception of the effect of urinary symptoms on HRQL, demonstrated that Flomax® provided greater improvement vs. terazosin

- No other α_1-adrenoceptor antagonist used to treat the signs and symptoms of BPH has a better safety profile than Flomax®

- In the pivotal trials, adverse events (AEs) with a higher incidence in Flomax® patients (including patients taking both 0.4 mg/day and 0.8 mg/day) relative to placebo included abnormal ejaculation, rhinitis, dizziness, and infection – each of these AEs were reported more frequently in patients taking Flomax® 0.8 mg/day
- No clinically significant effect on vital signs (i.e. sitting systolic and diabolic blood pressure and pulse rate) was found in patients receiving treatment with Flomax® who were hypertensive, or whose hypertension was controlled, or who were normotensive
- In long-term studies (up to six years of follow-up), clinically significant orthostatic hypotension was not observed in Flomax® patients
- In a head-to-head study comparing Flomax® to terazosin, the rate of study discontinuation due to AEs was higher in the terazosin group (6.6%) than in the Flomax® group (4.3%)
- In a study involving over 10,000 patients being treated with Flomax® in a general medical practice setting, suspected AEs were reported in only 171 (1.4%) of the cohort after 6 months of treatment
- Flomax® was assigned pregnancy category B by the FDA, whereas both doxazosin and terazosin were assigned pregnancy category C

5.2 Economic Value of Flomax

The economic value of Flomax® (tamsulosin hydrochloride) is tied to the fact that it is the only "prostate-specific" α_1-adrenoceptor antagonist, and that it has reduced affinity for α_1-receptors in the peripheral vasculature. As such, Flomax® has several characteristics that may lead to increased cost-effectiveness relative to the non-selective α_1-adrenoceptor antagonists, terazosin and doxazosin, including:

- Flomax® has a favorable side-effect profile, as it is associated with substantially lower rates of orthostatic symptoms (i.e. orthostatic hypotension, asthenia and syncope). In addition, Flomax® does not require titration to an effective dose. Therefore, Flomax® should have a reduction in or elimination of the following:
  - ★ side effects that may reduce patient adherence to therapy, thereby reducing effectiveness and increasing costs
  - ★ drug-induced hypotension that can lead to increased rates of sprains and fractures associated with falls
  - ★ complications with medical therapy in patients with concomitant hypertension
  - ★ titration that can affect costs due to more intensive effort (e.g. office visits) to manage medical therapy

The results from the cost-effectiveness analysis (see Section 4) can be utilized to estimate the budget impact to a health plan of switching patients from either doxazosin or terazosin to Flomax®. Table 8 provides scenario results, assuming that a cohort of 1,000 patients currently using either terazosin or doxazosin will be switched to Flomax®. Based on the cost-effectiveness model results using the "payer perspective" (see Table 6 -- with $7 co-pay for generic drugs and $15 co-pay for brand-name drugs), the proportion of patients achieving successful treatment was 7.7% higher for Flomax® than for either terazosin or doxazosin. Annual treatment costs were

lower for Flomax® than for the other two drugs. The resulting budgetary impact over a 2-year period of adding Flomax® to the formulary for the treatment of BPH would result in a savings ranging from $120,000 to $156,000.

Table 8. Budget Impact Summary

Scenario	Incremental annual savings per patient due to switch	Incremental # of patients successfully treated	Total budgetary impact (over 2-year period)
Switch cohort of 1,000 patients from doxazosin to Flomax®	$52	77	($156,000)
Switch cohort of 1,000 patients from terazosin to Flomax®	$40	77	($120,000)

Under an alternative scenario that does not take into account the reduction in payer costs due to patient co-pays, annual treatment costs were higher for Flomax® (incremental cost increase over 2-year period of $76 versus terazosin and $53 versus doxazosin). However, under this scenario, a monthly co-pay of approximately $3 would offset the cost of Flomax® for the payer.

5.3 Summary

In summary, Flomax® has been shown to be a safe and well-tolerated treatment option for effectively managing the signs and symptoms of BPH. In addition, Flomax® is the most cost-effective treatment option among the available α_1-adrenoceptor antagonists.

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ABBREVIATIONS

The following abbreviations are used throughout the document:

Abbreviation	Description
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ALF	Alfuzosin
AMPB	Ambulatory Blood Pressure
AUA	American Urological Association
AUC	Area Under the Curve
AWP	Average Wholesale Price
BID	Twice per day
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
CHO	Chinese Hamster Ovary
CI	Confidence Interval
DHT	Dihydrotestosterone
DRE	Digital Rectal Exam
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
HRQL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
I-PSS	International Prostate Symptom Score
IVP	Intravenous Pyelogram
LH	Leuteinizing Hormone
LUTS	Lower Urinary Tract Symptoms
MI	Myocardial Infarction

Abbreviation	Description
MRHD	Maximum Recommended Human Dose
NDC	National Drug Classification
NSAIDS	Nonsteroidal Antiinflammatory Drugs
OT	Orthostatic Stress Testing
PSA	Prostate Specific Antigen
QALY	Quality-Adjusted Life Year
QD	Once per day
Qmax	Maximum Urinary Flow
QOL	Quality of Life
RU	Resource Utilization
TAM	Flomax (tamsulosin)
TER	Terazosin
TID	Three times per day
TUMT	Transurethral Microwave Thermotherapy
TUNA	Transurethral Needle Ablation
TURP	Transurethral Resection of the Prostate
USP	United States Pharmacopoeia
UTI	Urinary Tract Infection

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